ASSESSMENT REPORT ON

ISOPROPANOL

FOR DEVELOPING AMBIENT AIR QUALITY OBJECTIVES

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ISOPROPANOL

FOR DEVELOPING AN AMBIENT AIR QUALITY OBJECTIVES

Prepared by
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IN CONJUNCTION WITH
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FOREWORD

Alberta Environment maintains Ambient Air Quality Objectives[1] to support air quality management in Alberta. Alberta Environment currently has ambient objectives for more than thirty substances and five related parameters. These objectives are periodically updated and new objectives are developed as required.

With the assistance of the Clean Air Strategic Alliance, a multi-stakeholder workshop was held in October 2000 to set Alberta's priorities for the next three years. Based on those recommendations and the internally identified priority items by Alberta Environment, a three-year work plan ending March 31, 2004 was developed to review four existing objectives, create three new objectives for three families of substances, and adopt six new objectives from other jurisdictions.

In order to develop a new three-year work plan, a multi-stakeholder workshop was held in October 2004. This study was commissioned in preparation for the workshop to provide background information on alternative, science based, and cost effective methods for setting priorities.

This document is one of a series of documents that presents the scientific assessment for these adopted substances.

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[1] **NOTE**: The *Environmental Protection and Enhancement Act*, Part 1, Section 14(1) refers to "ambient environmental quality objectives" and uses the term "guidelines" in Section 14(4) to refer to "procedures, practices and methods for monitoring, analysis and predictive assessment." For consistency with the *Act*, the historical term "ambient air quality guidelines" is being replaced by the term "ambient air quality objectives." This document was prepared as the change in usage was taking place. Consequently any occurrences of "air quality guideline" in an Alberta context should be read as "air quality objective."

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ACRONYMS, ABBREVIATIONS, AND DEFINITIONS

AAL	Allowable Ambient Level (Massachusetts) or Acceptable Ambient Level (North Carolina)
AAQC	Ambient Air Quality Criteria
AAS	Ambient Air Standard (Louisiana)
ACGIH	American Conference of Governmental Industrial Hygienists
AGC	Annual Guideline Concentration (New York State)
ANR	Vermont Agency of Natural Resources (Vermont)
ASIL	Acceptable Source Impact Level (Washington Department of Ecology)
ATC	Allowable Threshold Concentration – continuous exposure (daily lifetime) (Massachusetts DEP)
ATSDR	Agency for Toxic Substances and Disease Registry
bw	body weight
CalEPA	California Environmental Protection Agency
CAPCOA	California Air Pollution Control Officers Association
CAS	Chemical Abstracts Service
CCME	Canadian Council of Ministers of the Environment
CEIL	Ceiling Value
CEPA	Canadian Environmental Protection Act
DEC	Department of Environmental Conservation (eg., New York)
DENR	Department of Environment and Natural Resources (eg., North Carolina)
DEP	Department of Environmental Protection (eg., Massachusetts, New Jersey)
DES	Department of Environmental Services (eg., New Hampshire)
DEQ	Department of Environmental Quality (eg., Michigan, Louisiana, Oklahoma
DOE	Department of Environment or Department of Ecology (eg., Washington)
ENEV	Estimated No-Effects Value
EPA	Environmental Protection Agency (eg., Ohio)
ESL	Effects Screening Level
GLC	Ground Level Concentration
GV	Guideline Value
HAAS	Hazardous Ambient Air Standard
HEAST	Health Effects Assessment Summary Tables
HEC	Human Equivalent Concentration
HRV	Health Risk Value
IARC	International Agency for Research on Cancer
IHRV	Inhalation Risk Value
IRIS	Integrated Risk Information System
IRSL	Initial Risk Screening Level
ITSL	Interim Threshold Screening Level
LC50	Median Lethal Concentration
LD50	Median Lethal Dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEC	Lowest-Observed-Effect Concentration
LOEL	Lowest-Observed-Effect Level
MAAC	Maximum Acceptable Ambient Air Concentration

MAAQC	Maximum Annual Air Quality Criteria
MAC	Maximum Acceptable Concentration
MACT	Maximum Achievable Control Technology
MAGLC	Maximum Acceptable Ground-Level Concentration
MDH	Minnesota Department of Health
MHRV	Multimedia Health Risk Value
MIC	Maximum Immission Concentration (Netherlands)
MPR	Maximum Permissible Risk Level
MRL	Minimal Risk Level
MTLC	Maximum Tolerable Level Concentration
NAAQO	National Ambient Air Quality Objective
NIEHS	National Institute of Environmental Health Sciences (USA)
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-Observed-Adverse-Effect Level
NOEC	No-Observed-Effect Concentration
NOEL	No-Observed-Effect Level
NPRI	National Pollutant Release Inventory
NRCC	Natural Resource Conservation Commission
NTP	National Toxicology Program (USA)
OEHHA	Office of Environmental Health Hazard Assessment (California EPA)
OEL	Occupational Exposure Limit
OMOE	Ontario Ministry of Environment
OSHA	Occupational Safety and Health Association
PEL	Permissible Exposure Limit
PM	Particulate Matter
POI	Point of Impingement
PSL	Priority Substance List
PSL1	First Priority Substances List (Canada)
PSL2	Second Priority Substances List (Canada)
RD50	Median Respiration Rate Decrease
REL	Either Reference Exposure Limit as used by the California EPA or Recommended Exposure Limit used by both NIOSH and ATSDR
RfC	Reference Concentration
RfD	Reference Dose
RIVM	Netherlands Research for Man and Environment
RM	Risk Management
RTECS	Registry of Toxic Effects of Chemical Substances
SGC	Short-term Guideline Concentration
SRSL	Secondary Risk Screening Level
STEL	Short-term Exposure Limit
T-BACT	Best Available Control Technology for Toxics
TC	Tolerable Concentration
TCA	Tolerable Air Concentration
TC01	Tumorigenic Concentration - the concentration of a contaminant in air generally associated with a 1% increase in incidence or mortality due to tumours

TC05	Tumorigenic Concentration - the concentration of a contaminant in air generally associated with a 5% increase in incidence or mortality due to tumours
TD05	Tumorigenic Dose - the total intake of a contaminant generally associated with a 5% increase in incidence or mortality due to tumours
TEL	Threshold Effects Exposure Level
TLV	Threshold Limit Value
TNRCC	Texas Natural Resource Commission
TWA	Time-Weighted-Average
U.S. EPA	United States Environmental Protection Agency
WHO	World Health Organization

ppm	parts per million
ppb	parts per billion
mg	a milligram, one thousandth of a gram
µg	a microgram, one millionth of a gram
ng	a nanogram, one billionth of a gram

SUMMARY

Isopropanol is a colourless, clear, volatile liquid under standard conditions. It can react with air or oxygen to form unstable peroxides. Isopropanol can be manufactured from propene *via* either a strong acid process (no longer used in North America), a weak acid process, or a non-acid process. Isopropanol has widespread use as a solvent and as a component of many industrial, commercial and consumer products. Isopropanol is also a naturally occurring metabolic product in a variety of microorganisms and plants; as such, it occurs naturally in a wide variety of foods.

The main pathway of entry of isopropanol into the environment is through atmospheric emissions during production, handling, storage, transport, use, and disposal. In the ambient atmosphere, isopropanol is expected to exist solely as a vapour given its high vapour pressure. Atmospheric vapour-phase isopropanol degrades primarily *via* a reaction with photochemically-produced hydroxyl radicals. The atmospheric lifetime of isopropanol is short, approximately one to two days.

The major sectors in Alberta that release isopropanol to air are: minerals extraction, chemical manufacturing, and pharmaceutical manufacturing. Depending on the facility, releases of isopropanol to air occur *via* stack emissions, storage and handling, and fugitive emissions.

Isopropanol is rapidly absorbed into the bloodstream following inhalation exposure, and is rapidly distributed to all tissues of the body following absorption. It is metabolized *via* two biochemical pathways. The primary metabolic pathway involves the oxidation of isopropanol to acetone, mediated by the liver enzyme, alcohol dehydrogenase (ADH). A secondary metabolic pathway occurs *via* the conjugation of isopropanol with uridine diphosphate glucuronic acid or sulphates. Exhalation *via* the lungs is the primary route of elimination for isopropanol and its primary metabolite, acetone.

Isopropanol is an irritant and causes central nervous system depression with the major symptoms of acute intoxication including: irritation of upper respiratory tract, shortness of breath, dizziness, incoordination, headache, confusion, flushing, hypothermia, contracted pupils and eye ataxia.

Isopropanol is not currently considered to act as a carcinogen. The weight of available evidence from genotoxicity and mutagenicity studies strongly suggests that isopropanol is not a mutagen.

The review of the physical chemical properties (Section 2.0), and toxicology (Section 4.0) of isopropanol indicates several key benchmark air concentrations that should be considered in establishing an ambient air quality guideline for isopropanol. Odour thresholds for isopropanol are highly variable and have been reported to range from 3.9 to 5,446 mg/m^3, with most reported odour threshold concentrations ranging between 7.4 and 202 mg/m^3.

The acute toxicity of isopropanol is characterized primarily by upper respiratory tract irritation and central nervous system effects. Nelson *et al.* (1943) reported a LOAEL and NOAEL of 400 and 200 ppm (984 and 492 mg/m^3), respectively, in 10 human volunteers. This study has been used as the basis for all occupational exposure limits for isopropanol, as well as the OEHHA

(1999) acute reference exposure level (REL). A number of other acute human inhalation studies provide support for 984 mg/m^3 as an acute effects threshold for isopropanol. Smeets and Dalton (2002) reported that odour detection thresholds were well below current recommended occupational exposure limits, and the irritation thresholds were well above these values.

No data regarding the subchronic or chronic systemic toxicity of isopropanol to humans by any exposure route were identified. The animal study by Burleigh-Flayer *et al.* (1997) reported a NOAEL of 500 ppm. The OEHHA (2003) chronic REL of 3.0 ppm (7 mg/m^3) was developed from this NOAEL. No human reproductive studies were identified; only one animal study was identified that investigated the reproductive or developmental effects of isopropanol following inhalation exposure. Nelson *et al.* (1988) reported a LOAEL of 8,610 mg/m^3. Gentry *et al.* (2002) applied a PBPK model to derive an inhalation RfC for isopropanol. The recommended RfC from this modelling effort is 40 ppm (98 mg/m^3). The RfC incorporated a 30-fold uncertainty factor, and is based on the endpoint of decreased foetal body weights in rats and mice.

Relatively few jurisdictions have established an ambient air quality guideline for isopropanol. For those agencies with guidelines, the basis is either the ACGIH TLV-TWA or STEL values of 400 ppm (984 mg/m3) or 500 ppm (1,230 mg/m3), respectively (adjusted with various modifying and uncertainty factors), or the RfC values established by OEHHA (CalEPA). The OMOE and TNRCC criteria differ from the other jurisdictions reviewed in that they are based upon odour effects of isopropanol, rather than health effects data. All existing air quality guideline values appear to be adequately protective of human health. In addition, given the available data on the environmental fate, transport, and effects of isopropanol, this compound is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone, or alter precipitation patterns. Isopropanol has a relatively low reactivity in photochemical smog situations, and a low potential for ground level ozone formation.

1.0 INTRODUCTION

Alberta Environment (AENV) establishes Ambient Air Quality Objectives under Section 14 of the Environmental Protection and Enhancement Act (EPEA). These objectives are part of the Alberta Air Quality Management System (AENV, 2000).

Ambient Air Quality Objectives (AAQO) provide a basis for determining whether or not ambient air quality is acceptable from a health perspective. For substances lacking Alberta objectives, the development of acceptable ambient air concentrations typically considers a number of factors, including physical-chemical properties, sources, effects on human and environmental health, air monitoring techniques, and ambient air guidelines derived by other jurisdictions within Canada, the United States, various other countries, and multi-country organizations (*e.g.*, World Health Organization).

The main objective of this assessment report is to provide a review of scientific and technical information to assist in evaluating the basis and background for an AAQO for isopropanol. The following aspects were examined as part of this review:

- Physical and chemical properties,
- Existing and potential natural and anthropogenic emissions sources in Alberta,
- Effects on humans, animals, and vegetation,
- Monitoring techniques, and
- Ambient air guidelines in other Canadian jurisdictions, United States, European Union and Australia, and the basis for their development and use.

Key physical and chemical properties that govern the fate and behaviour of isopropanol in the environment are reviewed and presented in this assessment report. Existing and potential natural and anthropogenic sources of isopropanol air emissions in Alberta are also reviewed and presented in this report. This included information obtained from Environment Canada's National Pollutant Release Inventory (NPRI) and the National Air Pollution Surveillance Network (NAPS Network).

Scientific information regarding the toxic effects of isopropanol on humans and animals are reported in a number of sources, including toxicological and epidemiological studies published in peer-reviewed journals, and detailed regulatory agency reviews such as those published by the International Agency for Research on Cancer (IARC), World Health Organization (WHO), U.S. Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Environmental Protection Agency's (U.S. EPA) Integrated Risk Information System (IRIS) and Toxicological Profiles, and Canadian Priority Substance List Reports under CEPA 1999. There also is a recent air quality guideline scientific support document for isopropanol from the Ontario Ministry of the Environment (OMOE, 2002). These sources provide valuable information for understanding the potential human and environmental health effects of isopropanol. Key information from these sources regarding the effects of airborne concentrations of isopropanol on humans, animals, plants and the environment is summarized in this report.

Air monitoring and measuring techniques for isopropanol in air are well documented in the peer-reviewed scientific and regulatory agency literature. Several widely used and accepted air monitoring reference methods exist for isopropanol that have been developed, tested and reported by such agencies as U.S. EPA, U.S. National Institute of Occupational Safety and Health (NIOSH), and U.S. Occupational Safety and Health Administration (OSHA). These methods and techniques are summarized in this report.

2.0 GENERAL SUBSTANCE INFORMATION

Isopropanol is a colourless, clear, volatile liquid under standard conditions (ACGIH, 1992; WHO, 1990). Its odour has been described as pleasant (Lewis, 1997), a mixture of acetone and ethanol (WHO, 1990), and comparable to rubbing alcohol (NIOSH, 1994). Other sources have described the odour as sharp (AIHA, 1989). It has a slightly bitter, burning taste (Budavari *et al.*, 1996; Ellenhorn and Barceloux, 1988; WHO, 1990). The compound is completely miscible with water, other alcohols, ether, acetone, chloroform, and benzene, while it is considered insoluble in salt solutions (Budavari *et al.*, 1996; WHO, 1990). The compound undergoes all chemical reactions typical of secondary alcohols (WHO, 1990). This chemical can react with air or oxygen to form dangerously unstable peroxides. Contact with 2-butanone increases the reaction rate for peroxide formation (NTP, 2001). Isopropanol reacts violently with strong oxidizing agents such as chlorine, bromine, and fluorine (NJDHSS, 1997). Isopropanol is a highly flammable liquid at room temperature and standard atmospheric pressure (WHO, 1990; NTP, 2001). In a fire, it may decompose to form toxic gases, including carbon monoxide. A violent, explosive reaction occurs when it is heated with aluminum isopropoxide and crotonaldehyde (NTP, 2001). Isopropanol may corrode some forms of plastics, rubber and coatings (HSDB, 2003).

Table 1 provides a list of common synonyms, trade names, and identification numbers for isopropanol.

Isopropanol can be manufactured from propene *via* a strong acid process (indirect hydration), a weak acid process, or a non-acid process (Clayton and Clayton, 1994; WHO, 1990). Indirect hydration is based on a two-step reaction of propylene and sulphuric acid. In the first step, mixed sulphate esters, primarily isopropyl hydrogen sulphate and diisopropyl sulphate form; these compounds are then hydrolyzed, forming isopropanol and sulphuric acid (Kirk-Othmer, 1996). Acid-catalyzed direct hydration of propylene has three basic processes of commercial operation which are: (1) vapour-phase hydration over a fixed-bed catalyst of supported phosphoric acid or silica-supported tungsten oxide with zinc oxide promoter, (2) mixed vapour-liquid-phase hydration at low temperature and high pressure using a strongly acid cation-exchange catalyst, and (3) liquid-phase hydration at high temperature and high pressure in the presence of a soluble tungsten catalyst (Kirk-Othmer, 1996). The catalytic hydration process has largely replaced the strong acid and weak acid processes as a result of the potentially hazardous intermediates and by-products produced by the acid processes (WHO, 1990). The strong acid process is no longer used in North America, and has been largely replaced by the weak acid process. Other processes for production of isopropanol include: liquid phase oxidation of propane, reductive condensation of acetone, fermentation, and biological production from carbohydrate raw materials (Kirk-Othmer, 1996).

In 1975, the world production of isopropanol was estimated to be in excess of 1.1 million tonnes (WHO, 1990). The global production capacity of isopropanol in 1984 was estimated to be in excess of 2.2 million tonnes (WHO, 1990). It has been estimated that the major industrial and commercial uses of isopropanol are as follows: direct solvent uses (40%); chemical derivatives (27%); acetone production (15%); household and personal care products (10%); pharmaceuticals (5%); miscellaneous solvent and chemical intermediate uses (3%) (ChemExpo, 1998).

Table 1 Identification of Isopropanol

Property	Value
Formula	C_3H_8O
Structure	
CAS Registry Number	67-63-0
RTECS Number	NT8050000
UN Number	UN1219
Common Synonyms	2-hydroxypropane 2-propanol Isopropyl alcohol Dimethylcarbinol Sec-propanol Sec-propyl alcohol Propan-2-ol 2-propyl alcohol
Common Tradenames	AI3-01636 Caswell No 507 EPA Pesticide Chemical Code 047501 FEMA No 2929 Visco 1152 Alcojel, Alcosolve 2 Avantin(e) Chromar Combi-Schutz E 501 Hartosol Imsol A, IPS-1 Isohol Lutosol Petrohol Propol Spectrar Takineocol UN 1219

Isopropanol has widespread use as a solvent and as a component of many industrial, commercial and consumer products (WHO, 1990; HSDB, 2003; NTP, 2001). Its solvent applications are numerous and include the following: a process solvent (*e.g.*, extraction and purification of products such as vegetable and animal oils and fats, gums resins, waxes, colours, flavourings, alkaloids, vitamins, kelp and alginates, carrier solvent in the manufacture of food products, purification, crystallization and precipitation of organic chemicals), a coating and dye solvent (*e.g.*, phenolic varnishes, nitrocellulose lacquers, cements, primers, paints, inks), a cleaning/drying agent (*e.g.*, manufacture of electronic parts, metals processing, photography, paper products, glass cleaners, liquid soaps and detergents), a solvent for pharmaceutical and

cosmetic products (*e.g.*, rubbing alcohol, hair tonics, perfumes, skin lotions, hair care products, skin cleaners, deodorants, nail polishes, shampoos), an aerosol solvent (*e.g.*, cleaners, waxes, polishes, paints, de-icers, deodorizers, insect repellents, pesticides, hair sprays, deodorants, air-fresheners), and a solvent in medical and veterinary products (*e.g.*, antiseptics, first aid and medical vapour sprays, skin soothers, disinfectants, antipyretics) (OMOE, 2002; WHO, 1990; HSDB, 2003). This compound also is used in the preservation of pathological specimens and dehydration of tissues (WHO, 1990; NTP, 2001) and as a synthetic flavouring adjunct in non-alcoholic beverages (25 ppm), candies (10-75 ppm), and baked goods (75 ppm) (NTP, 2001; HSDB, 2003). In addition, isopropanol is used in the manufacturing of various other chemicals including acetone, glycerol and isopropyl acetate (Clayton and Clayton, 1994; WHO, 1990), and as a denaturant, a coolant in beer manufacturing, a coupling agent, a dehydrating agent, a polymerization modifier in the production of polyvinyl fluoride, a foam inhibitor, a heat-exchange fluid, and a component of windshield wiper fluid.

2.1 Physical, Chemical and Biological Properties

The physical and chemical properties of isopropanol are summarised in Table 2.

2.1.1 Environmental Fate

Based on its physical properties and use patterns, the main pathway of entry of isopropanol into the environment is through atmospheric emissions during production, handling, storage, transport, use, and disposal (WHO, 1990).

The environmental fate of isopropanol is summarized in Table 3. In the ambient atmosphere, isopropanol is expected to exist solely as a vapour given its high vapour pressure. Atmospheric vapour-phase isopropanol degrades primarily *via* a reaction with photochemically-produced hydroxyl radicals (HSDB, 2003). The half-life of this reaction is approximately 6.2 to 72 hours (Atkinson, 1987; Howard *et al.*, 1991). Isopropanol is not expected to react significantly with other reactive atmospheric oxidants such as ozone, and hydroperoxy-, alkyl-, and alkoxy-radicals (WHO, 1990). The major products formed from these atmospheric photooxidation reactions include acetone, acetaldehyde, peroxyacetyl nitrate, formaldehyde, methyl nitrate, and formic acid (Carter *et al.*, 1979). Atmospheric residence times of 1.4 to 2.3 days have been estimated for isopropanol, based on reaction with hydroxyl radicals (Cupitt, 1980). Since isopropanol does not absorb ultraviolet radiation within the solar spectrum, photolysis is an unlikely environmental fate process (Carter *et al.*, 1979). The short atmospheric lifetime of isopropanol prevents migration of the chemical into the stratosphere and greatly limits long-range atmospheric transport.

Transport of isopropanol from the atmosphere to soil or water surfaces occurs mainly by wet deposition, as isopropanol is highly soluble in water (WHO, 1990).

Isopropanol is not expected to hydrolyze in the environment as it lacks hydrolysable functional groups, nor is it predicted to directly photolyse due to the lack of absorption in the environmental UV spectrum (>290 nm) (HSDB, 2003). In photochemical smog, isopropanol has relatively low reactivity and exhibits a low potential to form ground level ozone (HSDB, 2003).

Since isopropanol is highly water soluble, it can be expected to be very mobile in soil (WHO, 1990; HSDB, 2003). Based on its tendency to volatilize, especially from moist surfaces, isopropanol is not expected to persist in either soil or water (HSDB, 2003). Isopropanol readily undergoes aerobic biodegradation in both soil and water for which the half-life ranges from 24 to 168 hours and 26 to 168 hours, respectively (Howard *et al.*, 1991). Isopropanol also may undergo anaerobic degradation. In water, isopropanol has a volatilization half-life for a model river and model lake of 57 hours and 29 days, respectively. Due to a low log K_{ow} and K_{oc} value, isopropanol is not predicted to adsorb to suspended solids and sediment to any significant extent (HSDB, 2003. Similarly, due to its low log K_{ow} value, the potential for bioconcentration and bioaccumulation in aquatic or terrestrial organisms is predicted to be negligible (HSDB, 2003).

Table 2 Physical and Chemical Properties of Isopropanol

Property	Value	Reference
Molecular Weight	60.10	Verschueren, 1983
Physical State	Liquid	Verschueren, 1983
Melting Point	-86/-89°C	Verschueren, 1983
	-88.5°C	Howard, 1990; NTP,2001; Budavari *et al.*, 1996
	-89.5°C	RAIS, 2003
Boiling Point	82.3°C	RAIS, 2003
	82.4°C	Verschueren, 1983; ACGIH, 1992
	82.5°C	Howard, 1990; Budavari *et al.*, 1996; NTP, 2001
Specific Gravity (liquid)	0.785 at 20°C	WHO, 1990; Budavari *et al.*, 1996
	0.7861 at 20°C	ACGIH, 1992
Specific Gravity (gas; air=1)	2.07	HSDB, 2003; WHO, 1990; NTP, 2001
Vapour Pressure	4.27 kPa at 20°C	Verschueren, 1983
	4.4 kPa at 20°C	WHO, 1990
	5.86 kPa at 25°C	NTP, 2001
	6.05 kPa at 25°C	HSDB, 2003; RAIS, 2003
	7.60 kPa at 30°C	Verschueren, 1983
Solubility in Water	1,000,000 mg/L at 22°C	NTP, 2001; WHO, 1990; HSDB, 2003
Solubility	Miscible with alcohol, chloroform, ether, and glycerol	NTP, 2001; HSDB, 2003
	Soluble in benzene	NTP, 2001; HSDB, 2003
	Insoluble in salt solutions	NTP, 2001; HSDB, 2003; Budavari *et al.*, 1996
Henry's Law Constant	8.10×10^{-6} atm.m^3/mole at 25°C	HSDB, 2003
Octanol Water Partitioning Coefficient (log K_{ow})	0.05	RAIS, 2003; HSDB, 2003
	0.14	WHO, 1990

Property	Value	Reference
Octanol Carbon Partitioning Coefficient (K_{oc})	25	HSDB, 2003
Flash Point (closed cup)	11.7°C	WHO, 1990; NJDHSS, 1997; ACGIH, 1992
Explosive Limits	2.0% to 12%	NTP, 2001
	2.3% to 12.7%	ACGIH, 1992
Autoignition Temperature	399°C	NTP, 2001; ACGIH, 1992
Odour Threshold	1.6 to 2,214 ppm (detection)	van Gemert, 1999
	3.2 to 82 ppm (recognition)	van Gemert, 1999
	7.5 ppm (recognition)	NTP, 2001
	3.3 ppm (perception)	WHO, 1990
	7.5 to 49.2 ppm (recognition)	WHO, 1990
	19 ppm (geometric mean)	AIHA, 1989
	22 ppm	Amoore and Hautala, 1983
	geometric mean odour detection threshold: exposed workers - 39 ppm controls - 11 ppm	Smeets and Dalton, 2002
Bioconcentration Factor in Fish	3	HSDB, 2003
Conversion Factors for Vapour (at 25°C and 101.3 kPa)	1 ppm = 2.46 mg/m^3 1 mg/m^3 = 0.41 ppm	WHO, 1990

Table 3 Environmental Fate of Isopropanol (based on Mackay *et al.*, 1992; HSDB, 2003; Howard *et al.*, 1991)

System	Fate	Half-life
Water	Loss by volatilization and anaerobic biodegradation; adsorption to sediment or suspended particulate matter, bioconcentration in aquatic organisms and reactions with hydroxyl radicals in water are all negligible	*Volatilization*: 57 hours (model river) and 29 days (model lake) *Anaerobic biodegradation*: 26 to 168 hours
Soil	Loss *via* volatilization from dry and moist soils and anaerobic biodegradation; negligible adsorption; high mobility; potential for leaching	*Anaerobic biodegradation*: 24 to 168 hours
Air	Exists solely as a vapour; degradation *via* reaction with hydroxyl radicals; exhibits a low potential to form ozone in photochemical smog	*Photochemical reactions with hydroxyl radicals*: 6.2 to 72 hours

3.0 EMISSION SOURCES, INVENTORIES, AND AMBIENT AIR CONCENTRATIONS

3.1 Natural Sources

Isopropanol is a naturally occurring metabolic product in a variety of microorganisms and plants (WHO, 1990; OEHHA, 2003). As such, it occurs naturally in a wide variety of foods.

3.2 Anthropogenic Sources and Emissions Inventory

3.2.1 Industrial

Production processes, as well as industrial, commercial and domestic sources and uses of isopropanol have been previously described in Section 2.0.

A total of 25 industrial facilities in Alberta reported on-site releases of isopropanol to the 2001 National Pollutant Release Inventory (NPRI) database. However, according to NPRI (2001), only seven reporting facilities in Alberta release isopropanol to the atmosphere. The remaining facilities that reported on-site releases of isopropanol, release to land. Two of the major reporting facilities for on-site releases (Chevron Canada's Kaybob South #3 gas plant and Acheson sour gas plant) released 9.17 tonnes (combined) to land in 2001. Also, for many facilities in Alberta that use or produce isopropanol, significant amounts are transferred off-site for disposal or recycling, and are not released directly to air, land or water (NPRI, 2001).

Table 4 provides total on-site releases for the seven facilities that release isopropanol to air, and Table 5 provides details on the air emissions for these facilities. The major sectors in Alberta that release isopropanol to air are: minerals extraction, chemical manufacturing, and pharmaceutical manufacturing. Depending on the facility, releases of isopropanol to air occur *via* stack emissions, storage and handling, and fugitive emissions.

3.3 Ambient Air Concentrations in Alberta

One study was identified which reported ambient air concentrations of isopropanol in Alberta. A survey conducted in the Town of Banff in November 2002 reported one-hour average isopropanol concentrations on two sampling days of 0.58 and 0.80 $\mu g/m^3$ (AENV, 2003).

Table 4 **Total On-site Releases (tonnes/year) of Isopropanol in Alberta (Seven Facilities) According to NPRI, 2001**

NPRI ID	Facility Name	City	Total Releases (tonnes)			
			Air	Land	Water	Total
1119	Banner Pharmacaps Ltd. - Banner Pharmacaps (Canada) Ltd.	Olds	6.51	0	0	6.51
5351	Baker Petrolite Corporation - Baker Petrolite Corporation	Calgary	1.34	0	0	1.34
5304	Champion Technologies Ltd. - Calgary Plant	Calgary	0.56	0	0	0.56
5245	Raylo Chemicals Inc. - Clover Bar Site	Edmonton	0.49	0	0	0.49
2340	Vopak Canada Ltd. - Calgary	Calgary	0.38	0	0	0.38
2349	Vopak Canada Ltd. - Edmonton	Edmonton	0.16	0	0	0.16
4567	Ondeo Nalco Energy Services Canada Inc. - Nisku Blend Plant	Nisku	0.10	0	0	0.10

Table 5 **Sources of Air Emissions of Isopropanol (tonnes) in Alberta (Seven Facilities) According to NPRI, 2001**

NPRI ID	Facility Name	City	Air Emissions (tonnes)					
			Stack/ Point	Storage/ Handling	Fugitive	Spills	Other	Total
1119	Banner Pharmacaps Ltd. - Banner Pharmacaps (Canada) Ltd.	Olds	6.51	0	0	0	0	6.51
5351	Baker Petrolite Corporation - Baker Petrolite Corporation	Calgary	0.17	0.75	0.41	0	0	1.34
5304	Champion Technologies Ltd. - Calgary Plant	Calgary	0	0.56	0	0	0	0.56
5245	Raylo Chemicals Inc. - Clover Bar Site	Edmonton	0.49	0	0	0	0	0.49
2340	Vopak Canada Ltd. – Calgary	Calgary	0	0.38	0	0	0	0.38
2349	Vopak Canada Ltd. – Edmonton	Edmonton	0	0.16	0	0	0	0.16
4567	Ondeo Nalco Energy Services Canada Inc. - Nisku Blend Plant	Nisku	0	0.10	0	0	0	0.10

4.0 EFFECTS ON HUMANS AND ECOLOGICAL RECEPTORS

4.1 Humans and Experimental Animals

The following toxicological review of isopropanol is focussed primarily on the inhalation route of exposure, as this is the predominant route of human exposure to isopropanol in air. Data on other exposure routes are included in this review only where relevant, or where inhalation exposure data are lacking. Where sufficient data are available, human studies are emphasized in this section. However, relevant experimental animal studies are included where human data is either lacking or inadequate.

4.1.1 Overview of Toxicokinetics of Isopropanol

Absorption

Isopropanol is rapidly absorbed into the bloodstream following inhalation exposure (WHO, 1990; HSDB, 2003; OEHHA, 2003). Rapid uptake in humans was demonstrated in a study of male workers that were occupationally exposed to isopropanol (Brugnone *et al.*, 1983).

Although quickly absorbed, the extent of isopropanol absorption and retention *via* the inhalation route appears to be quite low. Slauter *et al.* (1994) reported that 80 to 90% of the inhaled dose was rapidly exhaled by rats and mice. In a human study, Brugnone *et al.* (1983) reported that isopropanol was not detected in either the blood or urine of printing workers exposed to isopropanol concentrations between 8 and 647 mg/m^3, even though alveolar uptake increased linearly with increasing exposure levels (*i.e.*, 0.03 to 6.6 mg/min). Other animal studies also reported non-detectable concentrations of isopropanol in blood shortly after inhalation exposure to high concentrations of this substance. For example, Nelson *et al.* (1988) reported that blood levels in adult rats were not detectable following a single exposure at 7,636 mg/m^3. After 10 and 19 consecutive daily exposures, blood levels in adult rats were consistently not detected at the 7,636 mg/m^3 exposure level.

Distribution

As isopropanol is highly water soluble, it is expected to be rapidly distributed to all tissues of the body following absorption (WHO, 1990).

No specific information on distribution following inhalation exposure was identified in the available scientific literature. However, data from oral exposure studies in animals indicates that isopropanol, and its principal metabolite acetone, are detected in a variety of tissues and biological fluids including serum, spinal fluid, liver, kidneys, and brain (Agarwal, 1979; Natowicz *et al.*, 1985; Idota, 1985; Raichle *et al.*, 1976; Wax *et al.*, 1949).

Metabolism

In humans, isopropanol is metabolized *via* two biochemical pathways. The primary metabolic pathway involves the oxidation of isopropanol to acetone, mediated by the liver enzyme, alcohol dehydrogenase (ADH) (WHO, 1990). A secondary metabolic pathway occurs *via* the

conjugation of isopropanol with uridine diphosphate glucuronic acid or sulphates (WHO, 1990). This pathway forms isopropyl glucuronic acid (Slauter *et al.*, 1994). There is some evidence that endogenous formation of isopropanol can occur in humans, possibly from the reduction of acetone by liver ADH (Davis *et al.*, 1984; Lewis *et al.*, 1984; Tiess and Hammer, 1985). The endogenous formation of isopropanol in humans has been demonstrated from autopsies of individuals with no known exposure to this compound (WHO, 1990). Furthermore, studies with rats have shown that isopropanol can form from the reduction of acetone by liver ADH, especially when high levels of acetone and high NADH/NAD+ ratios occur (WHO, 1990). These conditions are found in subjects with diabetes mellitus, starvation, high fat intake, chronic alcoholism, and dehydration (De Ceaurriz *et al.*, 1981; Lewis *et al.*, 1984; Tiess and Hammer, 1985).

Figure 1 (obtained from WHO, 1990) depicts the metabolism and elimination of isopropanol in mammals (2-propanol is a synonym for isopropanol). Alcohol dehydrogenase appears to oxidize the majority of absorbed isopropanol to acetone, with acetone being further metabolized to acetate, formate, and ultimately carbon dioxide (OEHHA, 2003). In susceptible subjects (*e.g.*, diabetics, alcoholics, malnourished, *etc.*) the conversion of acetone to acetate and formate may lead to acidosis, and the metabolism of isopropanol also may shift the NAD/NADH ratio, which could lead to hypoglycaemia (Snyder, 1992).

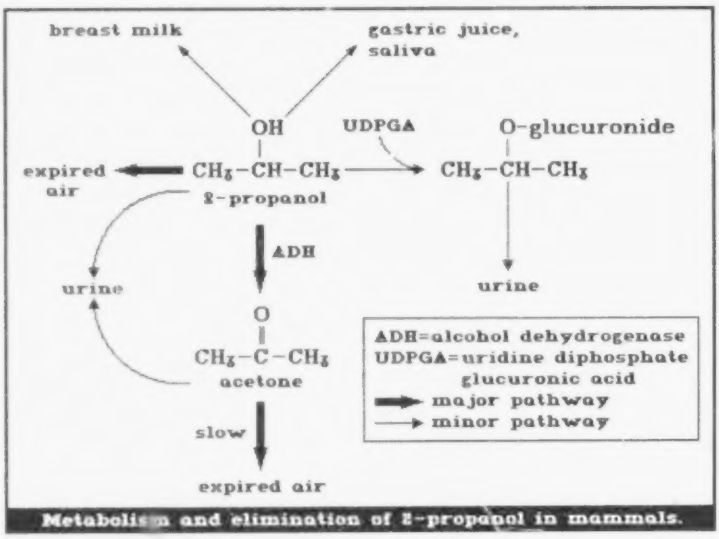

Figure 1 **Mammalian Metabolism and Elimination of Isopropanol (2-propanol) (WHO, 1990)**

Some studies have found that the amount of acetone in the blood stream is directly proportional to the external air concentration of isopropanol (Laham *et al.*, 1980). This finding suggests that the presence of acetone in the expired air, blood or urine of exposed subjects could be used as a biochemical indicator (or biomarker) of isopropanol exposure.

Support for the role of ADH in isopropanol metabolism in humans comes from studies reporting that concomitant exposure to ethanol (for which ADH has a greater affinity than isopropanol) retarded the formation of acetone (Idota, 1985), and detection of acetone in the blood, alveolar air and urine of exposed workers (Brugnone *et al.*, 1983). Furthermore, it is well established from numerous animal studies that isopropanol is metabolized primarily to acetone and carbon dioxide, as they have been identified in expired air in these studies (*e.g.*, Abshagen and Rietbrock, 1969; Idota, 1985; Laham *et al.*, 1979; Laham *et al.*, 1980; Nordmann *et al.*, 1973; Savolainen *et al.*, 1979; Siebert *et al.*, 1972; Slauter *et al.*, 1994). Also, as for humans, co-administration of ethanol and isopropanol has been reported to impair the metabolism and elimination of isopropanol in experimental animals (Abshagen and Rietbrock, 1970).

The disappearance of isopropanol from the blood follows a first-order rate process in experimental animals, although increasing half-lives observed at higher doses suggests that the metabolic pathways can become saturated (Abshagen and Rietbrock, 1969; Siebert *et al.*, 1972).

Elimination and Excretion

In both humans and experimental animals, exhalation *via* the lungs is the primary route of elimination for isopropanol and its primary metabolite, acetone (WHO, 1990). Acetone has been detected in exhaled air of human subjects at levels up to 40% of the administered dose (Brugnone *et al.*, 1983; Kemal, 1927; WHO, 1990). The minor metabolites (uridine diphosphate glucuronic acid conjugates or sulphates) are eliminated by urinary excretion (Bonte *et al.*, 1981; WHO, 1990). In metabolism studies with rats and mice, Slauter *et al.* (1994) found that up to 92% of the administered dose (*via* intravenous or inhalation routes) of isopropanol was exhaled as acetone, carbon dioxide, and un-metabolized isopropanol. This study also reported that approximately 3 to 8% of the administered dose was excreted in urine as isopropanol, acetone, and a metabolite tentatively identified as isopropyl glucuronic acid. An earlier study by Rietbrock and Abshagen (1971) found that urinary excretion of both isopropanol and its metabolite acetone, is limited and accounts for less than 4% of the administered dose in rats, rabbits, and dogs. Minor amounts of isopropanol have been found to be excreted *via* the gastric juice and saliva in the dog, and through breast milk in the rat (Lehman *et al.*, 1944; 1945).

The elimination of isopropanol in experimental animals follows first-order kinetics, which is believed to be the case for humans as well (WHO, 1990). No human inhalation half-lives were identified in the scientific literature; however, isopropanol half-lives (in blood) following ingestion exposure have been reported to range between 2.5 and 6.4 hours (Daniel *et al.*, 1981; Natowicz *et al.*, 1985). The half-lives of acetone in these studies were found to be longer (roughly 22 hours), and blood levels of acetone declined more slowly than those of isopropanol (up to 30 hours). Isopropanol half-lives (in blood) of 11 and five hours have been reported for dogs and rats, respectively (Abshagen and Rietbrock, 1969).

Prolonged administration of isopropanol (by any route) results in increased elimination rates of both un-metabolized isopropanol and acetone in dogs and rats (Lehman *et al.*, 1945; Savolainen *et al.*, 1979). However, in contrast, Slauter *et al.* (1994) observed no increased elimination rates for isopropanol or its metabolites, following repeated exposures.

Physiologically-Based Pharmacokinetic (PBPK) Modelling

Clewell *et al.* (2001) developed an interspecies PBPK model (rats and humans) that describes the absorption, distribution, metabolism and elimination of isopropanol, and its major metabolite, acetone. The model is capable of accounting for endogenous production of acetone as well. This model has been validated, and was recently used to derive a reference dose (RfD) and reference concentration (RfC) for isopropanol (Gentry *et al.*, 2002).

Biomarkers

Based on the observed correlation between alveolar, blood and urinary acetone levels in rats and humans, with external isopropanol exposure levels, the WHO (1990) concluded that acetone levels can be used for biological monitoring, as an indicator of isopropanol exposure.

Although isopropanol levels in the breath and saliva are equally well correlated with environmental isopropanol concentrations, the half-life of isopropanol is considered too short for this substance to be a useful biomarker of exposure (WHO, 1990). Kawai *et al.* (1990) studied urinary acetone and isopropanol concentrations in male and female printing industry workers exposed to up to 66 ppm (162 mg/m^3) isopropanol (as time-weighted average). Acetone and isopropanol concentrations in urine were also studied in 34 non-exposed subjects. There was concurrent exposure to toluene, xylenes, methyl ethyl ketone and/or ethyl acetate. Acetone was detectable in the urine of most of the exposed workers, and the urinary acetone concentration increased in proportion to the isopropanol exposure intensity. Adjusting urinary concentrations for creatinine or specific gravity had an insignificant effect on the relationship. Isopropanol was not detected in the urine of the non-exposed workers, and was detectable only in the urine of subjects exposed to air concentrations greater than 5 ppm (12 mg/m^3). The authors concluded that urinary acetone is a valuable index for biological monitoring of occupational exposure to isopropanol in air at concentrations as low 70 ppm (172 mg/m^3). Another study (Ghittori *et al.*, 1996) investigated urinary acetone levels in 80 male plastics factory workers. The mean time weighted average air concentration was 18 ppm (44 mg/m^3). The urinary acetone levels correlated significantly with airborne isopropanol concentrations. The authors found that the lowest airborne isopropanol concentration associated with an increase in urinary acetone concentration was 44 ppm (108 mg/m^3), and concluded that urinary acetone appears to be a useful indicator of occupational exposure to isopropanol.

Acetone concentrations in human saliva have also been shown to correlate well with isopropanol exposure levels (Tomita and Nishimura, 1982).

4.1.2 Acute Toxicity

The major symptoms of acute isopropanol intoxication include: irritation of upper respiratory tract, shortness of breath, dizziness, incoordination, headache, confusion, flushing, hypothermia, contracted pupils and eye ataxia (OEHHA, 1999; HSDB, 2003; Ellenhorn and Barceloux, 1988; WHO, 1990). Vomiting, hematemesis, diarrhoea, and hypotension may occur following ingestion of large quantities of isopropanol (HSDB, 2003). Extremely high intakes of isopropanol may result in aspiration pneumonia, respiratory depression, lung, spleen and liver congestion, tachycardia, severe confusion, severe hypotension, shock, impaired reflexes, kidney

and liver dysfunction, and coma (OEHHA, 1999; HSDB, 2003; Ellenhorn and Barceloux, 1988; WHO, 1990). Acute isopropanol intoxication has a rapid onset (less than one hour) and peak effects typically occur within several hours of exposure (HSDB, 2003). If serious nervous system effects occur, they may persist for up to 24 hours (HSDB, 2003). Some other reported symptoms of isopropanol intoxication may include: hyperglycaemia, elevated protein levels in cerebrospinal fluid, atelectasis, presence of acetone in the blood, urine, and breath, acetonaemia and/or acetonuria without metabolic acidosis, and a significant osmolality gap (WHO, 1990).

Nelson *et al.* (1943) conducted a study of ten human volunteer subjects that were exposed for 3 to 5 minutes to 200, 400 or 800 ppm (490, 980, and 1,970 mg/m^3) of isopropanol. After each exposure, the subjects were asked to classify the effects of the isopropanol vapour on their eyes, nose, and throat. Exposure to 400 ppm produced mild irritation of the eyes, nose, and throat. At the 800 ppm exposure level, irritation effects were more intense and the majority of the subjects declared the atmosphere unsuitable for a prolonged exposure, but that irritation was not "severe". An air concentration of 200 ppm was reported as "not objectionable" by the subjects. Given the subjective manner in which effects were evaluated in this study, and the lack of controls, its results are of questionable validity (WHO, 1990). However, this study is the basis for all current isopropanol occupational exposure limits, and many existing air quality guidelines.

A recent study by Sethre *et al.* (2000a) investigated the acute effects of isopropanol exposure on the performance of neurobehavioral functions in humans. Twenty healthy subjects were exposed to isopropanol at a concentration of 400 ppm (980 mg/m^3) in an exposure chamber for eight hours. Isopropanol was found to affect postural balance at this concentration. In a similar study, (Sethre *et al.*, 2000b), 10 isopropanol-exposed workers in a Swiss foundry were monitored for neurobehavioral effects for 15 days at 10 random times throughout their work day. The workers were exposed to isopropanol at an average environmental concentration of 44 ± 16 ppm (107.8 ± 39.2 mg/m^3). No neurobehavioral effects were observed in any of the workers tested.

Smeets and Dalton (2002) assessed intra-nasal irritation thresholds for isopropanol using the lateralization method. Twenty six occupationally exposed workers and matched controls provided subjective ratings of odour, irritation and annoyance intensity for three concentrations of isopropanol. The intra-nasal irritation threshold was elevated relative to controls (occurring at 6,083 ppm (15,000 mg/m^3)) in exposed workers *versus* 3,361 ppm (8,268 mg/m^3) in controls, with 95% of the workers experiencing no sensory irritation below 512 ppm (1,260 mg/m^3). This study also reported a geometric mean odour detection threshold of 39 ppm (96 mg/m^3) in exposed workers and 11 ppm (27 mg/m^3) in controls. The odour detection thresholds were well below the current recommended occupational exposure limits, and the irritation thresholds were well above these values.

Recently, van Thriel *et al.* (2003) investigated acute neurobehavioral effects during controlled exposure to isopropanol in young male volunteers (mean age = 25.8 years). The subjects were exposed in a 29 m^3 exposure chamber for four hours to isopropanol at two concentrations (34.9 and 189.9 ppm; 86 and 467 mg/m^3). The subjects consisted of 12 individuals with reported enhanced chemical sensitivity, and 12 age-matched controls. At the end of the high and low isopropanol exposures, tiredness ratings were elevated, but there was no dose-dependence observed. Annoyance ratings increased during the exposure in a dose-dependent manner. The

subjects reported olfactory symptoms, but isopropanol caused no sensory irritation. The authors concluded that the results of this study confirm previous studies reporting no neurobehavioral effects for isopropanol at concentrations up to 400 ppm (984 mg/m^3).

Table 6 summarizes the relevant acute human toxicity studies with isopropanol.

In rats and mice, inhalation LC50 values are reported to range from 46,740 to 72,600 mg/m^3 (Laham *et al.*, 1979; Guseinov, 1985). Exposure durations ranged from two to eight hours in these studies and observation periods were typically 14 to 15 days.

In these studies, rats and mice showed unspecified signs of respiratory irritation and died due to respiratory arrest, usually within 24 hours following exposure (WHO, 1990). Necropsy results indicated edema, haemorrhage, inflammation, and dystrophy in the interstitial tissues of parenchymal organs, and infiltration, edema, and thinning of the alveolar walls in the lungs (Laham *et al.*, 1979). Other acute studies have reported a four-hour rat LC50 of 16,000 ppm (39,000 mg/m^3) (Carpenter *et al.*, 1949), an eight-hour LC50 of 12,000 ppm (29,490 mg/m^3) (Smyth, 1956), and a 10-minute RD50 of 17,693 ppm (43,000 mg/m^3) for mice (Kane at al., 1980).

Table 6 Summary of Acute Human Toxicity Studies with Isopropanol

Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
3 to 5 minutes	490 980 1,970	- no "objectionable effects" - mild irritation of eyes, nose and throat - more severe irritation of eyes, nose and throat	Nelson *et al.*, 1943
8 hours	980	- neurobehavioral effects (effects to postural balance)	Sethre *et al.*, 2000a
15 days – during 10 random times	107.8 (± 39.2) average	- no neurobehavioral effects	Sethre *et al.*, 2000b
not provided	15,000 8,268 1,260 96 27	- irritation effects in occupationally exposed workers - irritation effects in non-occupationally exposed controls - no sensory irritations in 95% of occupationally exposed workers - odour detected by workers - odour detected by control group	Smeets and Dalton, 2002
4 hours	86 and 467	- olfactory symptoms but no neurobehavioral effects (in males including chemically sensitive individuals)	Van Thriel *et al.*, 2003

A study in which Sprague-Dawley rats of both sexes inhaled isopropanol for eight hours at concentrations between 19,680 and 64,206 mg/m^3, reported severe irritation of the mucous membranes and depression of the central nervous system (Laham *et al.*, 1980). The nervous system effects included ataxia, prostration, and narcosis. These effects were concentration and time-dependent. All rats that survived eventually recovered. Other effects reported in this study were transient paralysis of the hind limbs at exposure levels between 49,200 and 54,120 mg/m^3. No animals survived exposure greater than 44,280 mg/m^3, and death generally occurred within two days, with females dying earlier than males. Upon necropsy, rats exposed to non-lethal levels of isopropanol displayed congestion of the liver, lung, and spleen, which was most prominent in the males. At lethal exposure levels, acute pneumonitis, severe cytoplasmic degeneration of the liver, and edema of the lung, brain and spleen were observed. Hypothermia was also observed in all rats exposed to 19,680 mg/m^3 or higher isopropanol air concentrations.

Mice exposed to 3,250 ppm (8,000 mg/m^3) for approximately eight hours developed ataxia, prostration and narcosis (Rowe and McCollister, 1982).

The effects of isopropanol on the mucociliary system of the trachea and the middle ear were investigated by Ohashi *et al.* (1987a,b). Groups of 20 or 24 Hartley guinea pigs were exposed to isopropanol vapour at concentrations of 0, 969, or 13,382 mg/m^3 for 24 consecutive hours. Four animals from each of the three groups were killed after 12 hours, 24 hours, and at 3, 7, and 14

days post-exposure. A concentration-related deterioration of ciliary activity and mucosal degeneration was observed in both the trachea and in the middle ear. At the lower exposure level, the effects completely reversed within two weeks post-exposure, but persisted in animals exposed at the higher exposure level.

Gill *et al.* (1995) exposed rats for six hours to 0, 500, 1,500, 5,000, or 10,000 ppm isopropanol (0, 1,230, 3,690, 12,300 and 24,600 mg/m^3). Signs of narcosis and concentration-related decreases in motor activity were observed in rats exposed to 5,000 or 10,000 ppm. Slight decreases in motor activity were observed in males in the 1,500 ppm group. Animals in the 1,500 and 5,000 ppm exposure groups recovered from these motor activity effects within five hours. Prostration or severe ataxia, decreased arousal, slowed or laboured respiration, decreased neuromuscular function, hypothermia and loss of reflex function were observed at one and six hours following exposure to 10,000 ppm. Similar, but less severe effects were observed in animals in the 5,000 ppm exposure group at one hour post-exposure. The six hour no-observed-effect level (NOEL) for this study was 500 ppm (1,230 mg/m^3) isopropanol.

An acute threshold for CNS effects was observed in rats after a four hour exposure to 1,450 mg/m^3 using the method of flexor reflexes, or the "summation threshold method" (Alekperov and Guseinov, 1980).

4.1.3 Subchronic and Chronic Toxicity

No data regarding the subchronic or chronic systemic toxicity of isopropanol to humans by any exposure route were identified. However, a number of inhalation exposure animal studies have been conducted.

Burleigh-Flayer *et al.* (1994) investigated toxicological and neurobehavioral endpoints in rats and mice following 13 week inhalation exposures (six hours/day, five days/week) to 0, 100, 500, 1,500 or 5,000 ppm isopropanol (0, 246, 1,230, 3,690, and 12,300 mg/m^3). In rats, clinical signs of toxicity included swollen periocular tissue (females) at the highest concentration and perinasal encrustation (males) at concentrations of 500 ppm and above. Narcosis was noted in a few animals of both species during exposure to 5,000 ppm and 1,500 ppm. However, the affected animals became tolerant to the narcotic effects of isopropanol after week two of exposure. No significant neurobehavioral changes were observed in any test animals; however, increased motor activity was noted at week nine of exposure in female rats of the 5,000 ppm group. Rats in the 1,500 and 5,000 ppm groups had significant increases in body weight gain throughout most of the exposure period (there was an initial drop in the 5,000 ppm group). However, only the 5,000 ppm group (male and female rats) had a greater than 10% body weight gain compared to controls. Similar increases in body weight and body weight gain greater than 10% were noted in female mice in the 5,000 ppm group. The test animals in this study underwent a detailed pathological evaluation. No gross lesions were observed in any organs. Reported pathological findings included: an increase in mean corpuscular volume (rats and female mice) and increased mean corpuscular haemoglobin (male rats and female mice) at the 5,000 ppm exposure level, slight anaemia in all rats at week six only, a slight dehydration in female mice at the end of the study, 8% increase in relative liver weight in rats in the 5,000 ppm group, a 10 and 21% increase in relative liver weight in female mice at 1,500 and 5,000 ppm, respectively, and hyaline droplets

within kidneys of all male rats, which was not concentration-dependent and was most prominent in the 5,000 ppm group.

In a follow-up lifetime inhalation study, Burleigh-Flayer *et al.* (1997) exposed male and female CD-1 mice and Fischer 344 rats, to 0, 500, 2,500, or 5,000 ppm (0, 1,230, 6,150, or 12,300 mg/m^3) of isopropanol vapour for six hour/day, five days/week for 78 weeks (mice) or 104 weeks (rats). Transient signs of narcosis were observed at the higher concentrations. For male rats in the 5,000 ppm group, there was increased mortality and a decreased mean survival time relative to controls. Increases in body weight and/or body weight gain were observed for both male and female mice and rats in both the 2,500 and 5,000 ppm groups throughout the study. In addition, increased absolute and/or relative liver and kidney weight were observed for male and/or female mice and rats in the 2,500 and 5,000 ppm groups. Urinalysis showed changes in urine chemistry that were indicative of impaired kidney function (decreased osmolality, increased total protein, volume, and glucose) in male rats of the 2,500 ppm group, and in male and female rats in the 5,000 ppm group. Upon necropsy, the most significant lesions in rats occurred in the kidney, and included mineralization, tubular dilation, glomerulosclerosis, interstitial nephritis, interstitial fibrosis, hydronephrosis, and transitional cell hyperplasia. The study authors considered chronic renal disease to be the main cause of death for male and female rats exposed to 5,000 ppm and most of the male rats exposed to 2,500 ppm. Other effects observed in mice included an increased incidence of seminal vesicle enlargement in males in the 2,500 and 5,000 ppm groups. Microscopically, these lesions consisted of an increased incidence of ectasia (dilation) of the seminal vesicles. There was also slight renal tubular proteinosis noted in male and female mice in all groups, and renal tubular dilation was seen in female mice in the 5,000 ppm group. The reported NOEL for toxic effects in both rats and mice was 500 ppm (1,230 mg/m^3).

The same study team also conducted a 13-week neurobehavioral study in isopropanol-exposed female Fischer 344 rats (Burleigh-Flayer *et al.*, 1998). Rats were exposed to 0 or 5,000 ppm isopropanol (0 or 12,300 mg/m^3) for six hours/day, five days/week. Increased motor activity (as characterized by the summation of ambulation, rearing and fine movements) was observed four weeks following exposure to 5,000 ppm. This effect was noted to be reversible two days following cessation of exposure in a subgroup of rats that were exposed to isopropanol for only nine weeks. In the subgroup exposed for 13 weeks, reversal of the increased motor activity did not occur until two weeks post-exposure. The reversal of this effect was not complete until 42 days following post-exposure. Other observed effects included a significant increase in body weight and an increased incidence of swollen periocular tissue.

An earlier neurobehavioral study used 20 male Wistar rats/group exposed to 0 or 300 ppm isopropanol (0 or 738 mg/m^3) for six hours/day, five days/week, for up to 21 weeks (Savolainen *et al.*, 1979). Biochemical effects included reduced enzyme activity of superoxide dismutase and azoreductase in cerebellar homogenate at weeks 20 to 21. Acid protease activity in glial cells was increased up to week 10. Open-field tests showed sporadic changes in urination (10th week) and defecation (15th week). The authors also noted that isopropanol exposure appeared to depress stimulation activity (due to caffeine administration) at 15 weeks.

A subchronic neurotoxicity study (Teramoto *et al.*, 1993) exposed Jcl-Wistar rats for 20 weeks to up to 8,000 ppm isopropanol (19,680 mg/m^3), for eight hours/day, five days/week. It was found that motor and sensory nerve conduction velocity increased significantly following the 20-week exposure period. Exposure to 1,000 ppm (2,460 mg/m^3) had no effect on conduction velocity. In all rats, conduction velocities returned to normal following the end of the exposure period. No effect on nerve conduction was observed in rats at concentrations up to 19,700 mg/m^3 for eight hours per day, five days per week for 20 weeks (Nakaseko, 1990).

Guseinov (1985) exposed groups of rats to isopropanol vapour at concentrations of 0, 100, or 500 mg/m^3 for five days/week, four hours/day over four months. No deaths were reported in any exposure group. At the end of the four- month exposure period, growth was reduced by 10% and the respiratory rate was increased by 22% in the 500 mg/m^3 group. White blood cell counts were decreased at both exposure levels in an exposure-dependent manner. Decreases in hippuric acid excretion and total serum protein, and an increase in blood acetylcholine were also noted at both exposure levels. Blood glucose levels were decreased in the 500 mg/m^3 group. Histopathological examination revealed irritant effects on the respiratory system, such as thinning of the alveolar walls, perivascular infiltration, pneumonia, and bronchitis in the 500 mg/m^3 group. Other reported effects at this concentration included dystrophic changes and perivascular cell reactions in the liver, and follicular hyperplasia in the spleen.

Baikov *et al.* (1974) exposed groups of 15 rats (unknown strain and sex) to isopropanol vapour at concentrations of 0, 0.6, 2.5, or 20 mg/m^3 air for 86 days. No deaths were reported. At the highest exposure level, reported effects included changes in the latency period of unconditional reaction, an increase in the number of fluorescent leukocytes, an increase in sulfobromophthalein retention, and decreased blood levels of nucleic acids. Adverse histopathological effects were only seen at 20 mg/m^3 and included liver dystrophy, degenerative changes in the cerebral cortex, and spleen hyperplasia.

The WHO (1990) stated that these latter two studies lack a number of essential details concerning the protocols used, the effects observed, the incidence of these effects, and adequate statistical analysis.

Zahlsen *et al.* (1985) exposed Sprague-Dawley rats by inhalation to isopropanol at concentrations of 490, 4,920, or 19,680 mg/m^3 in air for six days/week, six hours/day, over two weeks. In the liver and kidneys, cytochrome P-450 and cytochrome b_5 activity were increased as well as the activity of NADPH cytochrome c reductase at both the 4,920 and 19,680 mg/m^3 exposure levels. These effects were completely reversible in rats after a four-week recovery period. However, they persisted in the kidneys. The authors also reported that glutathione concentrations in the liver and kidneys increased slightly at these concentrations.

Table 7 summarizes the relevant subchronic and chronic isopropanol inhalation toxicity studies conducted with experimental animals.

Table 7 Summary of Subchronic and Chronic Isopropanol Inhalation Toxicology Studies in Experimental Animals

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Rats	6 h/d; 5 d/wk for 13 wks	12,300 1,230 12,300 12,300	- swollen periocular tissue (females); - perinasal encrustation (males) - no significant neurobehavioral effects - increased motor activity in female rats	Burleigh-Flayer *et al.*, 1994
Mice	6 h/d; 5 d/wk for 13 wks	12,300	- no significant neurobehavioral effects	Burleigh-Flayer *et al.*, 1994
Mice	6 h/d; 5 d/wk for 78 wks	NOAEL: 1230	- no toxic effects	Burleigh-Flayer *et al.*, 1997
Rats	6 h/d; 5 d/wk for 104 wks	NOAEL: 1230	- no toxic effects	Burleigh-Flayer *et al.*, 1997
Rats	8 h/d; 5 d/wk for up to 20 wks	2,460	- no effects on motor and sensory nerve conduction velocity	Teramoto *et al.*, 1993
Rats	8 h/d; 5 d/wk for up to 20 wks	19,700	- no effects on nerve conduction velocity	Nakaseko, 1990
Rats	4 h/d; 5 d/wk for over 4 months	500 100	- 10% reduction in growth and 22% increase in respiration; irritant effects on respiratory system - decreased white blood cell counts	Guseinov, 1985
Rats	86 d	20	-neurobehavioral and biochemical effects	Baikov *et al.*, 1974

4.1.4 Developmental and Reproductive Toxicity

No human reproductive studies were identified that investigated the reproductive or developmental effects of isopropanol following inhalation exposure.

Nelson *et al.* (1988) conducted what appears to be the sole developmental and reproductive inhalation study for animals. The investigators exposed pregnant rats to 0, 3,500, 5,000, 7,000, and 10,000 ppm (0, 8,600, 12,300, 17,000, and 25,000 mg/m^3) isopropanol for seven hours/day on days one to 19 of gestation. At concentrations of 7,000 ppm or greater, rats displayed signs of maternal toxicity, as indicated by reduced weight gain. Signs of narcosis were observed at the 10,000 ppm exposure level, but became slight by the end of the 19 day exposure period. An initial unsteady gait was noted in rats exposed to 7,000 ppm, which became unnoticeable by the end of the experiment. Foetal weight was reduced in all four exposure groups in a dose-dependent manner, but was only statistically significant in the two highest exposure groups. Increased foetal resorptions and reduced foetal weights (59% of controls) occurred at the highest exposure level. Foetal weights were also significantly reduced (85% of controls) at 7,000 ppm. A slight reduction in foetal weight (96% of controls) occurred at 3,500 ppm. Skeletal malformations (primarily rudimentary cervical ribs) were observed only at the two highest exposure levels. The highest exposure group also had six mated rats that were not pregnant at term. This was attributed to an exposure-related effect on implantation success. No teratogenic

effects were observed in the 3,500 ppm group. As there were minor developmental effects (slightly reduced foetal weight) seen at 3,500 ppm (8,610 mg/m^3), this exposure level is considered a LOAEL.

There are a number of reproductive/developmental studies of isopropanol administered *via* the oral route. Bates *et al.* (1994) reported no maternal toxicity or foetal neurotoxicity in rats administered 1,200 mg/kg bw/day. Other oral studies have indicated decreased foetal body weights and maternal weight gain, as well as reduced food consumption in rats (at 1,200 mg/kg bw/day) and rabbits (at 480 mg/kg bw/day) following either gavage or drinking water exposure to isopropanol (Tyl *et al.*, 1994; U.S. EPA/OTS, 1992a,b).

Using a multi-generational study design with rats, Bevan *et al.* (1995) exposed rats to 0, 100, 500 and 1,000 mg/kg body weight/day by oral gavage. Thirty rats (P1) were initially exposed for 10 or more weeks prior to mating. The mating period was up to three weeks in duration. Exposure continued throughout mating, parturition and lactation for the females and until delivery of the last litter for the males. P2 adults were selected from F1 litters and dosed for 10 to 13 weeks prior to mating. A single F2 litter was obtained from each P2 mating. Reproductive and developmental effects were evaluated for P1, P2, F1 and F2 animals. Reported effects included decreased male mating index (P2), decreased rat pup body weights (F1 and F2), and increased pup mortality (F1, F2) at the 1,000 mg/kg dose level only. Other reported effects included increased relative kidney and liver weight, and altered liver histopathology (adults only) at 1,000 mg/kg bw/day. The study authors determined a NOAEL of 500 mg/kg body weight day from this study. However, the U.S. EPA viewed reductions in postnatal survival at 100 mg/kg body weight/day as significant and dose-related and concluded that 100 mg/kg body weight/day was the NOAEL. Allen *et al.* (1998) applied the benchmark dose (BMD) approach to the results of the Bevan *et al.* (1995) study. The most relevant benchmark dose levels reported are 416 mg/kg/day for reduced male mating index, or 418 mg/kg/day for F2 survival rate. These benchmark dose levels lie between the conflicting NOAELs suggested by the U.S. EPA and Bevan *et al.* (1995).

An 18-week study spanning pre-mating, mating, gestational and post-partum periods (U.S. EPA/OTS, 1986), in which isopropanol was administered *via* drinking water, reported a NOEL of 0.5%. On a dose basis, this corresponded to 325, 520 and 1,200 mg/kg bw/day for males pre-mating, females pre-mating and females post-mating, respectively. The NOEL was based on hematological effects, altered organ and body weights and water and food consumption in the parents, and on decreased foetal body weight gain in the offspring. Reduced pup survival and litter size was also reported at the highest dose. However, no detailed teratogenic examination was performed on the pups, which limits the value of this study.

Recently, Gentry *et al.* (2002) applied the PBPK model developed by Clewell *et al.* (2001) to derive an oral RfD and inhalation RfC for isopropanol. The toxicity studies included in the modelling were Gill *et al.* (1995), Burleigh-Flayer *et al.* (1994; 1997; 1998), Tyl *et al.* (1994), and Bevan *et al.* (1995). The recommended RfD and RfC from this modelling effort are 10 mg/kg body weight/day and 40 ppm (98 mg/m^3), respectively. Both values incorporated a 30-fold uncertainty factor, and both values are based on the endpoint of decreased foetal body

weights. Endogenous acetone production was not accounted for in this study. It should be recognized that these toxicity values have not yet been endorsed by any regulatory agency.

4.1.5 Genotoxicity and Mutagenicity

Isopropanol has tested negative in bacterial mutation assays (*S. typhimurium* strains TA 98, TA100, TA 1525, and TA 1537), with and without metabolic activation (Florin *et al.*, 1980). Statistically significant numbers of mitotic aberrations have been reported in rat bone marrow cells after rats were exposed for four months to isopropanol vapour at concentrations of 0, 1.03, or 10.2 mg/m^3 air for four hours/day (Aristov *et al.*, 1981). However, the validity of this study's results is questionable as the authors did not report the number of rats exposed, their sex, or strain (WHO, 1990).

Isopropanol has produced negative results (with and without metabolic activation) in sister chromatid exchange tests (V79 Chinese hamster lung fibroblasts and Chinese hamster ovary cells) (Von der Hude *et al.*, 1987; Kapp *et al.*, 1993), and did not induce micronuclei in the bone marrow of mice in an *in vivo* study that exposed mice *via* intraperitoneal injection to doses from 350 to 2,500 mg/kg body weight (Kapp *et al.*, 1993). Chen *et al.* (1984) reported a dose-related increase in the inhibition of metabolic cooperation in hamster V79 cells. However, the authors believed this effect was due to membrane perturbation effects of the isopropanol, and reflects potential carcinogen promotion ability rather than direct genotoxic potential. Isopropanol also produced negative results in a fungal assay for aneuploidy (IARC, 1999).

Based on their own study findings and the weight of available evidence from other studies, Kapp *et al.* (1993) concluded that isopropanol is not a mutagen.

4.1.6 Carcinogenicity

A number of occupational epidemiology studies have been conducted on workers involved in either the manufacturing or use of isopropanol in various industrial processes.

A retrospective cohort study of 182 workers at a U.S. plant that manufactured isopropanol by the strong acid process over the period 1928 through 1950 was conducted by Weil *et al.* (1952). In a subgroup of 71 men employed for more than five years, seven cases of cancer were observed: four cancers of the paranasal sinuses, one lung carcinoma, one laryngeal carcinoma, and one laryngeal papilloma. The minimum latency period in this subgroup was six years. According to USA cancer statistics for 1948, 0.0014 paranasal sinus cancers would have been expected for the total cohort (Wright, 1979).

Hueper (1966) reported two cases of paranasal sinus cancer and two cases of laryngeal cancer in a cohort of 779 workers in a similar isopropanol plant in the USA that had been in operation since 1927. The minimum latency period in this study was 10 years. Age- and sex-adjusted incidence rates of sinus and laryngeal cancers in this group were 21 times higher than expected, based on comparison to national incidence rates.

A similar retrospective cohort study of 262 men who had worked for at least one year in an isopropanol plant (strong acid process) in the United Kingdom over the period 1949 to 1976 was

conducted by Alderson and Rattan (1980). The follow-up period averaged 15.5 years. Contrary to the studies by Weil *et al.* (1952) and Hueper (1966), mortality rates due to all causes, and due to cancer were not significantly higher than expected according to national vital statistics. One worker died from nasal cancer against 0.02 expected. This study also reported two kidney and adrenal malignancies and two cancers of the brain and the central nervous system.

Another retrospective cohort study was conducted over the years 1966 to 1978 among 433 workers in an isopropanol manufacturing plant in the USA (Enterline, 1982). All workers were exposed for at least three months during the period 1941 to 1965. The strong acid process used at this plant in 1941 had been gradually changed to the weak acid process by 1965. The mortality rate due to all causes was lower than expected on the basis of State vital statistics. There was no excess mortality due to all cancers combined, but the incidence of buccal and pharyngeal cancer was four times higher than expected (two cases *versus* 0.5 expected). There was also a slight excess of lung cancer reported (seven *versus* 5.94 expected).

While these cohort studies appear to be suggestive of an increased risk of respiratory tract cancers in workers at isopropanol plants using the strong acid process, the fact that none of these studies quantified isopropanol exposure levels, or controlled for concurrent exposure to other chemicals or smoking rates among workers, greatly limits their interpretation. There is no established exposure-response relationship for isopropanol in any of these studies. In addition, later studies provided convincing evidence that the likely causative agent for the observed cancers was not isopropanol, but was likely diisopropyl sulphate, an intermediate produced in the strong acid process (WHO, 1990). It is also important to recognize that the strong acid process has not been widely used at isopropanol plants for approximately 40 years. The levels of diisopropyl sulphate are much lower in the weak acid process than they were in the strong acid process (Enterline, 1982).

Two small case-control studies of workers in a chemical plant and a rubber plant have also been conducted. Checkoway *et al.* (1984) investigated the risk of lymphocytic leukaemia associated with 24 solvents among rubber industry workers, while Leffingwell *et al* (1983) studied the risk of brain gliomas associated with work at a chemical plant. Neither study produced evidence of an association between exposure to isopropanol and the incidence of gliomas or lymphocytic leukaemia. However, small numbers of subjects and failing to control for concurrent exposures to other chemicals limits the conclusions that can be made from these studies.

A few animal studies investigating the carcinogenic potential of isopropanol have also been conducted.

Weil *et al.* (1952) exposed groups of three-month-old, male C3H, ABC, and C57/BL mice to isopropanol vapour at a concentration of 7,700 mg/m^3 for three to seven hours per day, five days/week, over a period of five to eight months. Surviving mice were killed and examined for the occurrence of lung tumours. Interestingly, mice were not examined for the occurrence of sinus tumours that were reported in isopropanol plant workers by these same authors. There was no excess of lung tumours observed in the mice. This study was criticized by WHO (1990) for a number of items, including the length of exposure period (eight months is insufficient in a carcinogenesis bioassay), and the inconsistent reporting of key experimental details in some of

the experiments, such as size of experimental and control groups, sex ratios, and length of post-exposure observation periods. Because of these shortcomings, this study is considered inadequate for the assessment of carcinogenic potential. (WHO, 1990)

Burleigh-Flayer *et al.* (1997) exposed CD-1 mice and Fischer 344 rats to isopropanol at 0, 500, 2,500 or 5,000 ppm (0, 1,230, 6,100 or 12,300 mg/m^3), six hour/day, five days/week for 78 weeks (mice) and 104 weeks (rats). The only observed increase in tumour incidence was a low incidence of interstitial cell adenoma in the testes of the male rats from all exposure groups, including controls. This increase was not considered to be dose-related. No increased tumour incidence was noted in mice (either sex) or female rats. The NOEL for interstitial cell adenomas was considered to be greater than 5,000 ppm (12,300 mg/m^3) in both mice and rats.

IARC (1999) reviewed the available studies investigating the carcinogenicity, genotoxicity and mutagenicity of isopropanol and has concluded that there is inadequate evidence for the carcinogenicity of isopropanol in humans, and in experimental animals. As such, isopropanol is not classifiable as to its carcinogenicity to humans (Group 3).

Neither the U.S. EPA nor Health Canada has classified isopropanol as to its carcinogenicity.

4.2 Effects on Ecological Receptors

Aquatic Life

In general, isopropanol is of relatively low toxicity to aquatic organisms. Isopropanol was found to inhibit cell multiplication of blue algae (*Microcystis aeruginosa*) and green algae (*Scenedesmus quadricauda*) after eight days of static exposure to 1,000 and 1,800 mg/L, respectively, in a closed system at 27°C and a pH of 7 (Bringmann, 1975; Bringmann and Kuhn, 1977).

A concentration of 141 mg/L was reported as the NOEC for water fleas (*Daphnia magna*) exposed to isopropanol for 16 days in a semi-static test at 19°C and a water hardness of 100 mg $CaCO_3$/L (Hermens *et al.*, 1985). EC50 values for *D. magna* ranged from 2,285 mg/L to 9,714 mg/L in one to four-day static tests (WHO, 1990). LC50 values for freshwater fish species range from 4,200 mg/L in Harlequin fish *(Rasbora duncker)* (Tooby *et al.*, 1975), to 11,160 mg/L in fathead minnow (*Pimephales promelas*) (Mattson *et al.*, 1976; Veith and Kosian, 1983) in static and flow-through tests of 24 to 96 hour durations. In brine shrimp (*Artemia salina*), a static 24 hour LC50 value of 10,000 mg/L was reported (Price *et al.*, 1974). In brown shrimp (*Crangon crangon*), 96 hour LC50 values ranging from 750 to 1,950 mg/L were reported (Blackman, 1974; Verschueren, 1983).

Insects

Insects also appear to be quite tolerant of isopropanol. A four-hour LC50 for third instar mosquito larvae *(Aedes aegypti)* of 25,120 mg/L was reported in a static test at 22 to 24°C (Kramer *et al.*, 1983). Forty-eight hour LC50 values for the fruit fly strains, *Drosophila melanogaster* and *Drosophila simulans* were between 10,200 and 13,340 mg/L of nutrient medium in static tests (David and Bocquet, 1976).

Plants

Plants also appear to have a high tolerance for isopropanol. Total inhibition of barley grain germination occurred after incubation for four days at 18°C on filter papers absorbing 39,420 mg isopropanol/L water (Chvapil *et al.*, 1962). The germination of white amaranth *(Amaranthus albus)* seeds was not affected after five hours of incubation at 25°C on filter papers moistened with a solution containing 36,050 mg/L isopropanol (Chadouef-Hanrel and Taylorson, 1985). Reynolds (1977) reported 50% inhibition of germination in lettuce *(Lactuca sativa)* seeds after incubation for three days at 30°C on agar containing 2,100 mg/L isopropanol. At 6,000 mg/L, complete inhibition of germination occurred. However, above 18,030 mg/L, germination was again observed and reached a maximum of 62% at 26,440 mg/L. A 28-day study on cell suspensions of root sections of soybean *(Glycine max)*, at 26°C and a pH of 5.6, found delayed onset of growth for one and two weeks at isopropanol concentrations of 10,000 and 20,000 mg/L of nutrient medium, respectively (Davis *et al.*, 1978).

4.2.1 Other Environmental Effects

Based on the available data on the environmental fate, transport, and effects of isopropanol, this compound is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone, or alter precipitation patterns. Farley (1977) and Yanagihara *et al.* (1977) reported that isopropanol has a relatively low reactivity in photochemical smog situations and a low potential for ground level ozone formation. Some of the products of photooxidation reactions of isopropanol with hydroxyl radicals (*e.g.*, peroxy acetyl nitrate, formic acid, acetaldehyde, formaldehyde) are known irritant components of photochemical smog.

4.3 Summary

Extensive studies and reviews of isopropanol toxicity have been conducted under Section 4 of the U.S. Toxic Substances Control Act. These data have been summarized by Kapp *et al.* (1996). In general, the data show that isopropanol is of low acute and chronic toxicity, does not produce adverse effects on reproduction or development, and is not genotoxic or carcinogenic. However, isopropanol is considered a potential hazard for transient central nervous system depression at high exposure levels. Isopropanol has produced effects to several rodent toxicity endpoints at high dose levels (*i.e.*, motor activity, male mating index, and renal lesions); however, these are of unclear relevance to human health. Isopropanol causes a significant narcotic effect upon exposure at high levels for extended periods of time, with no irreversible effects even after repeated exposure, which is consistent with other short-chain aliphatic alcohols. The metabolism of isopropanol appears similar across all species tested with rapid conversion to acetone and ultimately, carbon dioxide. Overall, isopropanol is considered to be a low potential hazard to human health (Kapp *et al.*, 1996). The review of the inhalation toxicology of isopropanol in Section 4.0 supports this conclusion. In addition, isopropanol is of relatively low toxicity to aquatic and terrestrial ecological receptors.

It should be recognized however, that isopropanol is capable of potentiating the toxicity of other organic chemicals if significant co-exposure is occurring. Aliphatic alcohols with 10 or fewer

carbon atoms are well known to potentiate the toxicity of a number of other organic chemicals, particularly chlorinated aliphatic compounds (Ray and Mehendale, 1990). This may be an important consideration in situations where there is concurrent exposure to both aliphatic alcohols and chlorinated aliphatics.

Based on a review of current and/or ongoing research and/or assessment activities or programs overseen by Health Canada, Environment Canada, Canadian Council of Ministers of the Environment (CCME), U.S. National Toxicology Program (NTP), U.S. National Institutes of Environmental Health Sciences (NIEHS), U.S. National Institute of Health CRISP Database, various U.S. EPA offices and programs (*e.g.*, TSCA, Science Advisory Board reports, *etc.*), Chemical Industries Institute of Toxicology (CIIT), Toxicology Excellence for Risk Assessment (TERA), World Health Organization (WHO), Agency for Toxic Substances and Disease Registry (ATSDR), and Health Effects Institute (HEI), there appear to be no current or ongoing studies or reviews specifically related to the toxicology of isopropanol under the direction of these agencies and institutes.

5.0 AIR SAMPLING AND ANALYTICAL METHODS

This section assesses the various air monitoring methodologies to measure isopropanol in ambient air, and describes their advantages and disadvantages.

5.1 Background

5.1.1 Introduction

Air monitoring is used to determine the concentrations of chemical species in the atmosphere. For any single chemical species, there are typically several methods that can be used, with varying detection levels, sampling periods/frequencies and operational levels-of-effort. Specific air monitoring methods include continuous, integrated passive, grab sampling and integrated active (Lodge, 1988). Many factors must be considered in selecting the best approach based on the overall objectives of the monitoring program. Considerations include minimum detection levels, measurement precision, averaging period and cost.

5.1.2 General Monitoring Approaches

In continuous monitors, a sample of air is drawn past a fast response detector using a pump. The detector produces an electrical signal that is proportional to the concentration of a specific chemical compound. Hourly average concentration information can be recorded by a digital data collection system (*i.e.*, a computer) or other storage medium (chart recorder).

In integrated passive sampling, a reactive surface in a controlled diffusion path is exposed for a nominal period ranging from 24 hours to one-month. The reactive surface is analyzed in a chemical laboratory to determine the concentration of the captured compounds. The method is termed passive because pumps are not drawing an air sample past a detector or through a collection medium.

In grab sampling, a whole air sample is collected in a non-reactive steel canister or plastic bag. The air sample is then analyzed in a laboratory to determine the concentration of the compounds in the air sample. Grab samples typically represent samples collected over the course of a few minutes to several hours.

In integrated active sampling, a known volume of air is drawn through a column filled with an absorbent material (for gases) or a collection filter (for particles) using a pump. These absorbent columns or filters are then analyzed in a laboratory to determine the concentrations of the collected compounds. Integrated samples are typically collected once every six days for a 24-hour period.

Integrated samplers require a sorbent to entrap the chemical species being sampled. The selection of the sorbent will depend on the specific compounds being sampled. Commonly used sorbents include, but are not limited to, Tenax, XAD-2, activated charcoal, Carbotrap C, Anasorb 747, Carbosieve, or a multi-stage combination using more than one sorbent. Dewulf and Langenhove (1997) describe four criteria that can be used in the selection of an appropriate sorbent. Firstly, it is important that the sampled compounds to not breakthrough the sorbent and

that the specific retention volume of the sorbent is known. Secondly, the sorbent cannot influence the sample by causing unwanted reactions with the sample. Thirdly, it is imperative that the sorbent not be contaminated prior to and after the sampling process. And lastly the retention of water on the sorbent should be small to avoid any interference with the laboratory analysis of the sample.

5.1.3 Laboratory Analysis

Collected samples (grab sampling) or sample media (integrated sampling) are analyzed to determine the respective concentrations. The most common process uses a gas chromatograph (GC) coupled to an appropriate detector. The GC process requires the sample to be placed in a heated chamber and purged with inert gas (*e.g.* helium) to separate and transfer the VOC sample from the sorbent, through a cold trap, onto the front of the GC column, which is initially at a low temperature. The GC column is heated to elute individual compounds based on their retention time (Lodge, 1988). The GC is usually coupled to an appropriate detector. Based on the required specificity and sensitivity of the application, there are several specific and non-specific detectors that can be used.

Non-specific detectors include the nitrogen-phosphorous detector (NPD), the flame ionization detector (FID), the electron capture detector (ECD) and the photo-ionization detector (PID) (U.S. EPA, 1999a). These detectors are generally less costly per analysis than specific detectors and can be more sensitive for specific classes of compounds. For example, if multiple halogenated compounds are targeted, using the ECD would provide more accurate identification. The non-specific detectors are coupled to the GC and individual compounds are identified by their retention time. The downside of using non-specific detectors is that they are prone to greater margins of error since they rely on retention times alone for compound identification. Also, there is a chance that interference can occur due to non-targeted compounds (U.S. EPA, 1999a).

Specific detectors include the linear quadrupole mass spectrometer (MS) and the ion trap detector. Both of these detectors are mass spectrometers. The mass spectra for individual peaks in the ion chromatogram are analyzed for the fragmented mass patterns of the primary and secondary ions. These fragmentations are compared to known spectra observed under like conditions. Based on the GC retention time and the mass spectral characteristics, each VOC in the sample can be determined.

Mass spectrometry is a more accurate method of determining specific compounds in ambient air samples because of their range of precision and simple identification process. Although the non-specific detectors have some advantages such as lower cost and higher sensitivity, the U.S. EPA (1999b) stresses that mass spectrometry is considered a more definitive identification technique and reduces the chances of misidentification.

5.1.4 Information Sources

Standardized air monitoring methods are documented by the U.S. Environmental Protection Agency (U.S. EPA), the Occupational Safety and Health Administration (OSHA), and the National Institute of Occupational Safety and Health (NIOSH). These agencies provide detailed approaches required to adequately measure hazardous air pollutants (HAPs) in ambient and

workplace air using a variety of air monitors and analysis techniques. Other information sources (*e.g.* technical journals, conference proceedings) were also reviewed to explore other air monitoring technologies, as well as new or emerging technologies.

5.1.4.1 U.S. EPA

The U.S. EPA has developed several air toxics methodologies for sampling VOC in ambient air. Detailed descriptions of these methods are available on the U.S. EPA Technology Transfer Network (TTN) – Ambient Monitoring Technology Information Center (AMTIC). The following U.S. EPA air toxics methods can be used to sample isopropanol:

- Compendium Method TO-17: Determination of volatile organic compounds in ambient air using active sampling onto sorbent tubes (U.S. EPA, 1999b).

According to the U.S. EPA, Compendium Method TO-17 is the only method that can be used to sample and analyze isopropanol. The following describes method TO-17 in detail.

U.S. EPA Compendium Method TO-17

Method TO-17 is a thermal desorption based ambient air monitoring method for VOC and is applicable for 0.5 and 0.25 ppbv ambient concentration levels. The U.S. EPA provides a list of compounds for which this method can be used based on sampling performance. These compounds are a subset of the 97 VOCs that are listed as hazardous air pollutants in the 1990 amendments of the U.S. Clean Air Act. Isopropanol is among those compounds that can be determined.

This method uses single or multi sorbents packed in tubes in order of increasing sorbent strength, allowing for a wide volatility range of VOC to be sampled. Using multi-sorbent tubes, compounds with higher molecular weights are retained first, and compounds with lower molecular weights last. If a single sorbent is being used, it should be specific to the target compound. Because of the specificity of certain sorbents, the thermal desorption process is very efficient.

The sample is drawn through a tube containing the selected sorbents. The isopropanol adsorbs to the sorbents while unwanted VOC and most other inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

5.1.4.2 NIOSH

NIOSH has developed several air toxics methodologies for sampling VOC in workplace air. Detailed descriptions of these methods are contained in the NIOSH Manual of Analytical Methods (NMAM). It should be noted that the NMAM was intended to achieve consistent industrial hygiene analyses and was not designed specifically for ambient air. The following NIOSH analytical method can be used to sample isopropanol:

- NIOSH Manual of Analytical Methods, Fourth Edition, Method 1400: Alcohols I (NIOSH, 1994).

- NIOSH Manual of Analytical Methods, Fourth Edition, Method 2549: Volatile Organic Compounds (Screening) (NIOSH, 1996).

Isopropanol can be sampled and analyzed using either of these two methods. Method 1400 is for alcohols while method 2549 is for VOC, both of which include isopropanol. The following section describes both NIOSH methods in detail.

NIOSH Method 1400

Method 1400 employs an activated charcoal (prepared from coconut shells) based solid sorbent tube which is a commonly used sorbent because its reactive surface promotes higher adsorptive capacity. It also has a very high area to weight ratio, which allows for higher sampling capacity.

The sample is drawn through a tube containing the activated charcoal sorbent. The isopropanol would adsorb to the charcoal sorbent while other highly volatile organic compounds and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

NIOSH Method 2549

Method 2549 is a general screening method for VOC. It employs a thermal desorption tube containing graphitized carbons and carbon molecular sieve sorbents. Multiple sorbents are packed in tubes in order of increasing sorbent strength, allowing for a wide volatility range of VOC to be sampled. Using multi-sorbent tubes, compounds with higher molecular weights are retained first, and compounds with lower molecular weights last. If a single sorbent is being used, it should be specific to the target compound. Because of the specificity of certain sorbents, the thermal desorption process is very efficient.

The sample is drawn through a tube containing the selected sorbents. The isopropanol adsorbs to the sorbents while unwanted VOC and most other inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

5.1.4.3 OSHA

OSHA has developed several air toxics methodologies for sampling VOCs in workplace air. Detailed descriptions of these methods are available from the Directorate of Science, Technology and Medicine (DSTM): Salt Lake Technical Center (SLTC). It should be noted that these methods were intended to provide a uniform and practical means for evaluating workplace air quality and were not designed specifically for ambient air. The following OSHA analytical methods can be used to sample isopropanol:

- OSHA Sampling and Analytical Methods, Organic Method 7: Organic Vapors (OSHA, 2000).
- OSHA Sampling and Analytical Methods, Organic Method 109: Isopropyl Alcohol (OSHA, 1997).

Organic Method 7 can be applied to a range of organic compounds whereas Organic Method 109 is limited to isopropanol. Organic Method 7 is a very general sampling method and provides a list of compounds that can be determined. Unlike other sampling methodologies, OSHA usually provides methods for individual and grouped compounds. For example, Method 109 describes the best available sampling method for isopropanol. The following sections describe both OSHA methods.

OSHA Method 7

Method 7 is a general organic vapour sampling methodology. It uses an activated charcoal based solid sorbent tube similar to that described in NIOSH Method 1400. Activated charcoal (prepared from coconut shells) is a commonly used sorbent because its reactive surface promotes higher adsorptive capacity. It also has a very high area to weight ratio, which allows for higher sampling capacity.

The sample is drawn through a tube containing activated charcoal sorbent. The isopropanol adsorbs to the charcoal sorbent while other highly volatile organic compounds and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

OSHA Method 109

Method 109 is a thermal desorption based method, which has a reliable quantitation limit of 44.4 ppb isopropanol. To ensure a maximum recovery, the sorbent used in this method is a 60/40 *N,N*-dimethylformamide/carbon disulphide solution. The use of this sorbent eliminates any excess water that may cause interferences with the sampling method.

A known volume of air is drawn through two Anasorb 747 tubes containing the sorbent to which the isopropanol adsorbs while other highly volatile organic compounds and most inorganic components pass through the tubes. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

5.1.4.4 Alternative and Emerging Technologies

The combination of the U.S. EPA, NIOSH, and OSHA ambient air sampling methods provides a broad scope of approaches. The sampling methods described in this section are designed for use over an eight-hour to 24-hour period. No additional alternative or emerging technologies for sampling isopropanol in ambient air were identified. As new and emerging technologies are developed, agencies such as the U.S. EPA provide information to users ensuring that the best available environmental practices are upheld.

6.0 EXISTING AMBIENT GUIDELINES

Current recommended or proposed isopropanol ambient air quality guidelines from selected regulatory agencies in Canada (other than Alberta), the United States and elsewhere are summarized in Table 8. Appendix A contains further information on each of these existing guideline values.

In general, all jurisdictions reviewed have common uses for their ambient air quality guidelines, including:

- Reviewing permit applications for air emission sources;
- Investigating accidental releases or community complaints about adverse air quality for the purpose of determining follow-up or enforcement activity;
- Conducting health risk assessments of industrial facilities and airsheds; and
- Monitoring and controlling ambient air quality.

The development of ambient air quality guidelines is driven by numerous societal and scientific issues, which require consideration of numerous factors such as aesthetics, property damage, toxicology, and ecology. Odour, for example, is an issue of aesthetics, and for chemicals with particularly objectionable odours, guideline values may be driven by odour thresholds, while for airborne chemicals that are corrosive, damage to structures may be a key consideration.

In terms of toxicology, air quality guidelines typically consider basic toxicological principles, which dictate that the response of an organism is a function of the magnitude of the dose and the duration over which the dose is received. The nature of the response of organisms (*i.e.,* the target tissues or organs and the toxicological endpoints) is another important consideration. For example, chemicals that act as primary respiratory irritants may have guidelines developed that are protective of these types of effects. Where toxicity concerns relate to non-respiratory targets (*e.g.,* liver or kidney) or to toxicological endpoints of late onset (*e.g.,* cancer, reproductive), air quality guidelines may be established to be protective of these types of effects. Chemicals that have multiple toxicological endpoints in more than one tissue or organ may have guidelines developed that are protective of the most sensitive toxic effects. Another consideration is the estimated or actual degree of exposure of key receptors to the air pollutant, particularly receptor groups that may exhibit sensitivity to the air pollutant (*e.g.*, elderly, asthmatics, children, *etc.*). Other important considerations in establishing an air quality guideline include the available technologies (and their costs) for routinely or periodically monitoring for the pollutant in air, and the availability and technical feasibility of approaches for estimating ambient ground-level air concentrations, in order to compare to air quality guidelines.

The three most common approaches by which ambient air quality guidelines are developed are as follows:

1. Using an occupational exposure level (OEL) and dividing it by safety or uncertainty factors, and amortizing for continuous exposure. These factors are intended to account for differences between eight-hour exposures in the workplace and continuous environmental exposures, increased susceptibility of individuals in the general population *versus* the

relatively healthy worker, and uncertainties in the margin of safety provided in an occupational exposure limit. It should be recognized however, that the use of OEL values has its limitations. For example:

- OELs are based on human effects information in industrial settings and may not accurately reflect ambient environmental exposure situations.
- OELs are derived to be protective of workers who are typically considered in good health and within the age range of 18 to 65 years. Such individuals are potentially less sensitive and/or susceptible to the effects of airborne pollutants than members of the general population. Among the general populations, there may be subpopulations or individuals that are more sensitive or susceptible to the effects of an airborne pollutant (*e.g.*, elderly, young children, asthmatics, people with pre-existing respiratory conditions, *etc.*)
- Worker exposures are typically based on a normal work schedule (eight hours per day, five days per week). For this work schedule, there are two days per week (weekends) in which the body may eliminate much of the accumulated substances before the next work-week begins. However, for individuals continuously exposed to an air pollutant in the ambient environment, there is no similar period when no exposure occurs.
- For these reasons, agencies using OELs as the basis for ambient air quality guidelines typically adjust OELs by applying safety or uncertainty factors.

2. Threshold chemical risk assessment procedures: Used for chemicals that are not believed to act as carcinogens and that exhibit a clear toxicity threshold. In this approach, a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) from a suitable animal or human study is divided by a series of uncertainty factors that account for issues such as: differences between animals and humans, sensitive individuals, use of a LOAEL instead of a NOAEL, and for extrapolation from subchronic to chronic exposure durations.

3. Non-threshold chemical risk assessment procedures: Used for substances believed to act as carcinogens. Cancer potency estimates, slope factors, tumorigenic potency values *etc.* are used to establish ambient air levels based on acceptable levels of incremental lifetime cancer risk, such as one in 100,000. These acceptable levels are established by regulatory agencies.

Finally, the potential ecological impacts of airborne chemicals also are important considerations in the guideline-setting process. Although a chemical may have no direct impact on human health or property, transfer of the chemical from the air to the terrestrial and aquatic environments by dry or wet deposition could have ecological impacts, depending on the physical, chemical and toxicological properties of the substance.

Current occupational exposure limits for isopropanol derived by ACGIH, NIOSH and OSHA are all based on the study by Nelson *et al.* (1943). These agencies all consider isopropanol to be of low toxicity by any route, and the airborne concentration limits are all based on eye, nose and throat irritation reported in human volunteers in Nelson *et al.* (1943). The current ACGIH TLV-TWA, OSHA PEL-TWA, and NIOSH REL values are all 400 ppm (983 mg/m^3). ACGIH (1992) states that this air concentration is expected to minimize the potential for narcotic effects or irritation of the eyes and/or upper respiratory tract, and would not be expected to cause central

nervous system depression. Chronic effects are not believed to result from exposure to concentrations below the TLV-TWA. Short-term or ceiling exposure levels have also been established for isopropanol by these agencies. The current STEL value from ACGIH, OSHA and NIOSH is 500 ppm (1,230 mg/m^3). ACGIH (1992) reports that occupational exposure limits from other countries are similar. For example, Australia, Germany and the United Kingdom (U.K.) use a threshold value of 400 ppm. Australia and the U.K. use a 10-minute STEL of 500 ppm. Germany uses a 30-minute STEL of 800 ppm (1,968 mg/m^3). Sweden uses an occupational limit of 150 ppm (369 mg/m^3) and a 15-minute short term value of 250 ppm (615 mg/m^3).

NIOSH (2003) reports an immediately-dangerous-to-life-and-health (IDLH) value of 2,000 ppm (4,900 mg/m^3). The IDLH is based strictly on safety considerations and is 10% of the lower explosive limit of 2%. Thus, it does not represent an appropriate basis for establishing an ambient air quality guideline.

Only the California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (OEHHA) has developed human toxicity-based airborne ambient exposure levels for isopropanol. The acute REL (OEHHA, 1999) is 1.3 ppm (32 mg/m^3) and is considered protective against mild adverse effects. This value was derived from the study by Nelson *et al.* (1943) where the LOAEL was reported to be 400 ppm (984 mg/m^3) for irritation effects. A NOAEL of 200 ppm (492 mg/m^3) was implied, as subjects had indicated that exposure to 200 ppm was tolerable. OEHHA (1999) estimated a one-hour concentration of 13 ppm from this NOAEL using the following ratio [*i.e.*, 200 ppm x 0.067 h = C x 1 h]. An uncertainty factor of ten was applied to this value (10-fold for susceptibility of sensitive individuals) to yield the acute REL of 1.3 ppm (3.2 mg/m^3).

OEHHA (1999) also developed a Level Protective Against Severe Adverse Effects. In studies by Gill *et al.* (1995) and Burleigh-Flayer *et al.* (1994), six-hour NOAELs of 500 ppm isopropanol (1,230 mg/m^3) were reported. A cumulative uncertainty factor of 100 (10-fold to account for interspecies differences; 10-fold to account for sensitive individuals) was applied to the six-hour NOAEL and an equivalent one-hour exposure concentration was estimated using the equation [$C_n * T = K$, where n = 2]. In this equation, C is the concentration, T is time, K is the severity of the response, and "n" refers to the toxicity of a chemical being determined to a greater extent by exposure concentration than by duration (OEHHA, 1999). The resulting level protective against severe adverse effects is 12 ppm (29 mg/m^3).

The OEHHA (2003) chronic REL of 3.0 ppm (7 mg/m^3) is based on the NOAEL of 500 ppm (1,230 mg/m^3) reported in Burleigh-Flayer *et al.* (1997). A human-equivalent concentration of 90 ppm (221 mg/m^3) was derived from this NOAEL. A cumulative uncertainty factor of 30 (10-fold for intraspecies differences; 3-fold for interspecies differences) was applied to this value to yield the chronic REL. The OEHHA selected Burleigh-Flayer *et al.* (1997) as the principal study because it was the only chronic study available that utilized lifetime animal exposures. The kidney effects observed in this study were not seen in the subchronic studies, indicating that chronic exposure is necessary for development of these particular types of lesions. As reproductive and developmental effects are also reported in the toxicological database for isopropanol, OEHHA derived a comparative REL based on the study by Nelson *et al.* (1988), the only study of this type to utilize the inhalation route of exposure. The study LOAEL was 3,500

ppm (8,610 mg/m^3) and OEHHA determined that the average exposure duration at the LOAEL was 1,024 ppm (2,519 mg/m^3). The OEHHA calculated a human-equivalent concentration from this LOAEL of 2,519 mg/m^3, and applied a cumulative uncertainty factor of 100 (3-fold for LOAEL to NOAEL; 3-fold for interspecies differences; 10-fold for intraspecies differences) to yield a REL of 10 ppm (25 mg/m^3). This developmental REL was within an order of magnitude of the chronic REL for kidney lesions, but was higher. Thus, kidney lesions were maintained as the critical effect for the chronic REL.

For the most part, the guidelines presented in Table 8 below are derived based on either the ACGIH TLV-TWA or STEL values of 400 ppm (984 mg/m^3) or 500 ppm (1,230 mg/m^3), respectively (adjusted with various modifying and uncertainty factors), or the RfC values established by OEHHA (CalEPA). The OMOE and TNRCC criteria differ from the other jurisdictions reviewed in that they are based upon odour effects of isopropanol, rather than health effects data. In the available documentation from some agencies, the basis behind the air quality guideline is not specified. Further information on the scientific basis for these guidelines, the application of uncertainty factors, and the practical application of these guidelines by the respective agencies, is provided in Appendix A. As indicated in Appendix A, relatively few of the jurisdictions reviewed have established ambient air quality guidelines for isopropanol.

The air quality guideline values used by the jurisdictions listed in Table 8 can be split into short-term and long-term values. Short-term ambient air guidelines for isopropanol include half-hour, one-hour, eight-hour, and 24-hour averaging periods. Ontario is the only jurisdiction with an half-hour limit (24 mg/m^3). One-hour limits exist in California, New Jersey, New York, and Texas. The lowest one-hour guideline is 3.2 mg/m^3 (California and New Jersey), while the highest is 120 mg/m^3 (New York). Only Vermont cites an eight-hour limit, which is 98 mg/m^3. Twenty-four-hour guidelines exist in Michigan, Newfoundland and Labrador, New Hampshire, Oklahoma, Ontario, and Washington. These 24-hour guideline values range from 0.22 mg/m^3 (Michigan) to 98.3 mg/m^3 (Oklahoma). Long-term air quality guidelines in the jurisdictions reviewed are generally listed as annual ambient limits, or are stipulated for continuous lifetime daily exposure. These values range from 0.785 mg/m^3 (Texas) to 7.0 mg/m^3 (California, New Jersey, New York).

It should be noted that the considerable variability observed between guidelines is primarily the result of differences in the approaches used in their derivation. While there is generally good agreement with respect to the choice of toxicological studies and data used as the basis for the guidelines, jurisdictions use different averaging periods and apply unique sets of uncertainty and modifying factors and assumptions in guideline development. The decision to use a particular approach involves policy decisions in addition to scientific considerations.

Table 8 Summary of Existing Air Quality Guidelines for Isopropanol

Agency	Name of Guideline (Averaging Period)	Guideline Value (mg/m^3)	Basis of Guideline	Date of Guideline[a]
California Environmental Protection Agency, Office of Environmental Health Hazard Assessment	Acute REL (1 h) Chronic REL (continuous lifetime daily exposure)	3.2 7.0	Nelson *et al.*, 1943 Burleigh-Flayer *et al.*, 1997	1999 2003
Michigan Department of Environmental Quality	ITSL (24 h)	0.22	Not clearly specified in available documentation. Established by State toxicologists based on available inhalation toxicity data Rule 229 procedures.	2003
Newfoundland and Labrador Department of the Environment	AQS (24 h)	24.0	Not provided in available documentation.	2003
New Hampshire Department of Environmental Services	AAL (24 h) AAL (annual)	4.95 3.30	Based on ACGIH TLV-TWA of 400 ppm.	1997
New Jersey Department of Environmental Protection	Short term RfC (1 h) RfC (continuous lifetime daily exposure)	3.2 7.0	Based on RELs developed by CalEPA OEHHA	2003
New York State Department of Environmental Conservation	SGC (1 h) AGC (continuous lifetime daily exposure)	120 7.0	The SGC is based on the ACGIH TLV STEL of 500 ppm. The basis for the AGC is not stated but is derived by the Department to protect the general population from adverse inhalation exposure off-site.	2000
Oklahoma Department of Environmental Quality	MAAC (24 h)	98.3	Based on ACGIH TLV-TWA of 400 ppm.	2003
Ontario Ministry of Environment and Energy	AAQC (24 h) POI (1/2 h)	24.0 24.0	Both values are based on odour effects. Specific rationale not provided.	2001
Texas Natural Resource Conservation Commission	Short-term ESL(1 h) Long-term ESL (annual)	7.85 0.785	Based on odour nuisance potential - 50% of the odour threshold concentration.	2003
Vermont Agency of Natural Resources	HAAS (8 h)	98.0	Based on ACGIH TLV-TWA of 400 ppm.	2001
Washington Department of Ecology	ASIL (24 h)	3.3	Based on ACGIH TLV-TWA of 400 ppm.	1998

a Date guideline was either promulgated or date of last review/revision by agency.

7.0 DISCUSSION

Isopropanol may be mildly corrosive to some rubbers, plastics and coatings. While it is flammable and may react explosively with certain substances, this is a safety issue that is separate and distinct from health-based guideline development. Isopropanol is not currently considered to act as a carcinogen. IARC (1999) concluded that there is inadequate evidence for the carcinogenicity of isopropanol in humans, and in experimental animals. Neither the U.S. EPA nor Health Canada has classified isopropanol as to its carcinogenicity. Furthermore, the weight of available evidence from genotoxicity and mutagenicity studies strongly suggests that isopropanol is not a mutagen. As such, toxicological considerations for this substance should focus on non-cancer endpoints following acute and chronic exposure.

The review of the physical chemical properties (Section 2.0), and toxicology (Section 4.0) of isopropanol indicates several key benchmark air concentrations that should be considered in establishing an ambient air quality guideline. First, odour thresholds for isopropanol are highly variable and have been reported to range from as low as 1.6 ppm to as high as 2,214 ppm (3.9 to 5,446 mg/m^3), with most reported odour threshold concentrations ranging between 3 and 82 ppm (7.4 and 202 mg/m^3).

The acute toxicity of isopropanol is characterized primarily by upper respiratory tract irritation and central nervous system effects. Nelson *et al.* (1943) reported a LOAEL and NOAEL of 400 and 200 ppm (984 and 492 mg/m^3), respectively, in 10 human volunteers. This study has been used as the basis for all occupational exposure limits for isopropanol, as well as the OEHHA (1999) acute REL. A number of other acute human inhalation studies provide support for 400 ppm (984 mg/m^3) as an acute effects threshold for isopropanol. Smeets and Dalton (2002) reported that odour detection thresholds were well below current recommended occupational exposure limits, and the irritation thresholds were well above these values.

The animal studies by Gill *et al.* (1995) and Burleigh-Flayer *et al.* (1994) reported six-hour NOAELs of 500 ppm (1,230 mg/m^3). OEHHA (1999) developed a Level Protective Against Severe Adverse Effects based on these studies. No data regarding the subchronic or chronic systemic toxicity of isopropanol to humans by any exposure route were identified. The animal study by Burleigh-Flayer *et al.* (1997) also reported a NOAEL of 500 ppm. The OEHHA (2003) chronic REL of 3.0 ppm (7 mg/m^3) was developed from this NOAEL. No human reproductive studies were identified, and only one animal study was identified that investigated the reproductive or developmental effects of isopropanol following inhalation exposure. Nelson *et al.* (1988) reported a LOAEL of 3,500 ppm (8,610 mg/m^3). Recently, Gentry *et al.* (2002) applied a PBPK model developed by Clewell *et al.* (2001) to derive an inhalation RfC for isopropanol. The toxicity studies included in the modelling were Gill *et al.* (1995), Burleigh-Flayer *et al.* (1994; 1997; 1998), Tyl *et al.* (1994) and Bevan *et al.* (1995). The recommended RfC from this modelling effort is 40 ppm (98 mg/m^3). The RfC incorporated a 30-fold uncertainty factor, and is based on the endpoint of decreased foetal body weights. It should be recognized that while this RfC value is not yet endorsed by any regulatory agency, it corresponds well with existing isopropanol air quality guidelines from Vermont and Oklahoma.

All of the short-term guideline values summarized in Table 8 are considerably lower than the NOAEL of 200 ppm (492 mg/m^3) reported in Nelson *et al.* (1943). Therefore, all these values appear to be adequately protective of human health over their respective averaging periods. All the long-term values in Table 8 are well below the NOAEL and LOAEL values reported by Burleigh-Flayer *et al.* (1997) and Nelson *et al.* (1988), and also are well below the recently recommended inhalation RfC that was derived by Gentry *et al.* (2002). Thus, all the long-term air quality guideline values also appear to be adequately protective of human health.

It should be recognized that all air quality guidelines in Table 8 have the built-in assumption that all human exposure to isopropanol occurs *via* inhalation. They do not account for other sources, pathways and routes of isopropanol exposure. If isopropanol exposure was apportioned to reflect these, the values presented in Table 8 would decrease in proportion to the magnitude of the exposure from these other sources, pathways and routes. In addition, none of the agencies with air quality guidelines in Table 8 reported any special consideration of children or other sensitive individuals in air quality guideline development. Although, protection of such individuals is typically afforded by the application of uncertainty factors.

Based on the information reviewed, none of the agencies listed in Table 8 specifically acknowledged an ecological component in the development of air quality guidelines for isopropanol. In addition, given the available data on the environmental fate, transport, and effects of isopropanol, this compound is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone, or alter precipitation patterns. Isopropanol also has a relatively low reactivity in photochemical smog situations, and a low potential for ground level ozone formation.

8.0 REFERENCES

Abshagen, U. and Rietbrock, N. 1970. The mechanism of the 2-propanol oxidation. Naunyn-Schmiedebergs Archiv fur Pharmakologie und Experimentelle Pathologie 265:411-424 (In German). Cited in: WHO, 1990.

Abshagen, U. and Rietbrock, N. 1969. Elimination of 2-propanol in dogs and rats. Naunyn-Schmiedebergs Arch Pharmakol Exp Pathol. 264: 110-118 (in German). Cited in: WHO, 1990.

ACGIH (American Conference of Governmental Industrial Hygienists). 1992. Supplement: Isopropanol. In: Documentation of the threshold limit values and biological exposure indices. Sixth Edition. American Conference of Governmental Industrial Hygienists Inc., Cincinnati, OH. ISBN 1-936712-96-1.

AENV (Alberta Environment). 2000. Alberta Ambient Air Quality Guidelines. Environmental Sciences Division, Alberta Environment. Edmonton, AB. February 2000.

AENV (Alberta Environment). 2003. Air Quality Monitoring. Town of Banff, November, 2002. February 13th, 2003.

AEP (Alberta Environmental Protection). 1998. Air Toxics Management in Alberta. Air Emissions Branch, Air and Water Approvals Division, and Air Issues and Monitoring Branch, Chemicals Assessment and Management Division, Environmental Services, Alberta Environmental Protection. April 1998.

Agarwal, S.K. 1979. Non-acidotic acetonemia: a syndrome due to isopropyl alcohol intoxication. J Med Soc New Jersey. 76: 914-916. Cited in: WHO, 1990.

AIHA (American Industrial Hygiene Association). 1989. Odor thresholds for chemicals with established occupational health standards. AIHA :Akron, OH.

Alderson, M.R. and Rattan, N.S. 1980. Mortality of workers on an isopropyl alcohol plant and two MEK dewaxing plants. Br J Ind Med. 37: 85-89. Cited in: WHO, 1990.

Alekperov, I.I. and Guseinov, V.G. 1980. Toxicological characteristics of isopropanol as an industrial poison. All Union Foundation Conference on Toxicology, Moscow, 25-27 November 1980. Cited in: WHO, 1990.

Allen, B., Gentry, R., Shipp, A., and Van Landingham, C. 1998. Calculation of benchmark doses for reproductive and developmental toxicity observed after exposure to isopropanol. Reg Toxicol Pharmacol. 28: 38-44.

Amoore JE, and Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatiles for 2114 industrial chemicals in air and water dilution. J Appl Toxicol. 3(6):272-290.

Aristov, V.N., Redkin, Y.V., Bruskin, Z.Z., and Ogleznew, G.A. 1981. Experimental data on the mutagenous effects of toluene, isopropanol, and sulfur dioxide. Gig. Tr. Prof. Zabol., 25: 33-36 (in Russian). Cited in: WHO, 1990.

Atkinson, R. 1987. Structure-activity relationship for the estimation of rate constants for the gas-phase reactions of OH radicals with organic compounds. Int'l J Chem Kinetics. 19:799-828. Cited in: Mackay *et al.* 1992.

Baikov, B.K., Gorolova, O.E., Gusev, M.I., Novikov, Y.V., Yudina, T.V., and Sergeev, A.N. 1974. Hygienic standardization of the daily average maximal permissible concentrations of propyl and isopropyl alcohols in the atmosphere. Gig. i Sanit., 4: 6-13 (in Russian). Cited in: WHO, 1990.

Bates, H.K., McKee, R.H., Bieler, G.S., Gardiner, T.H., Gill, M.W., Strother, D.E., and Masten, L.W. 1994. Developmental neurotoxicity evaluation of orally administered isopropanol in rats. Fundam Appl Toxicol. 22:152-158.

Bevan, C., Tyler, T., Gardiner, T., Kapp, R., Andrews, L., and Beyer, B. 1995. Two-generation reproduction toxicity study with isopropanol in rats. J Appl Toxicol 15:117-223. Cited in: OEHHA, 2003.

Blackman, R.A.A. 1974. Toxicity of oil-sinking agents. Mar Pollut Bull. 5: 116-118. Cited in: WHO, 1990.

Bonte, W., Rudell, E., Sprung, R., Frauenrath, C., Blanke, E., Kupilas, G., Wochnik, J., and Zah, G. 1981. Experimental investigations concerning the analytical detection of small doses of higher aliphatic alcohols in blood in man. Blutalkohol. 18: 399-411 (in German). Cited in: WHO, 1990.

Bringmann, G. 1975. Determination of the harmful biological action of water-endangering substances through inhibition of cell multiplication in the blue alga Microcystis. Ges.-Ing. 96: 238-241 (in German). Cited in: WHO, 1990.

Bringmann, G. and Kuhn, R. 1977. Limiting values of the harmful action of water-endangering substances on bacteria (*Pseudomonas putida*) and green algae (*Scenedesmus quadricauda*) in the cell multiplication inhibition test. Z Wasser-Abwasser Forsch. 10: 87-98 (in German). Cited in: WHO, 1990.

Brugnone, F., Perbellini, L., Apostoli, P., Bellomi, M., and Caretta, D. 1983. Isopropanol exposure: Environmental and biological monitoring in a printing works. Br J Ind Med. 40:160-168. Cited in: WHO, 1990.

Budavari, S., O'Neill, M.J., Smith, A., Heckelman, P.A., and Kinneary, J.F. eds. 1996. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. 12th Edition. Merck and Co., Inc.: Whitehouse Station, N.J.

Burleigh-Flayer, H., Garman, R., Neptun, D., Bevan, C., Gardiner, T., Kapp, R., Tyler, T., and Wright, G. 1997. Isopropanol vapor inhalation oncogenicity study in Fischer 344 rats and CD-1 mice. Fundam Appl Toxicol. 36(2): 95-111.

Burleigh-Flayer, H., Gill, M., Hurley, J., Bevan, C., Gardiner, T., Kapp, R., Tyler, T., and Wright, G. 1998. Motor activity effects in female Fischer 344 rats exposed to isopropanol for 90 days. J Appl Toxicol. 18: 373-381.

Burleigh-Flayer, H.D., Gill, M.W., Strother, D.E., Masten, L.W., McKee, R. H., Tyler, T.R., and Gardiner, T. 1994. Isopropanol 13-week vapor inhalation study in rats and mice with neurotoxicity evaluation in rats. Fundam Appl Toxicol. 23(3): 421-428.

Carpenter, C.P., Smyth, H.F. Jr., and Pozzani, U.C. 1949. The assay of acute vapor toxicity and the grading and interpretation of results on 96 chemical compounds. J Ind Hyg Toxicol. 31(6): 343-346. Cited in: OEHHA, 1999.

Carter, W.P.L., Darnall, K.R., Graham, R.A., Winer, A.M., and Pitts, J.N. 1979. Reactions of C_2 and C_4 alpha-hydroxy radicals with oxygen. J Phys Chem. 83: 2305-2311. Cited in: WHO, 1990.

Chadoeuf-Hannel, R. and Taylorson, R.B. 1985. Anaesthetic stimulation of Amaranthus albus seed germination: interaction with phytochrome. Physiol. Plant. 65: 451-454. Cited in: WHO, 1990.

Checkoway, H., Wilcosky, T., Wolf, P., and Tyroler, H. 1984. An evaluation of associations of leukemia and rubber industry solvent exposures. Am J Ind Med. 5: 239-249. Cited in: WHO, 1990.

ChemExpo. 1998. Chemical Profile: Isopropanol (Dec 28, 1998). Available from database query page at http://www.chemexpo.com/news/profile981228.cfm. Cited in: HSDB, 2003.

Chen, T.-H., Kavanagh T.J., Chang, C.C., and Trosko, J.E. 1984. Inhibition of metabolic cooperation in Chinese hamster V79 cells by various organic solvents and simple compounds. Cell Biol Toxicol. 1: 155-171. Cited in: WHO, 1990.

Chvapil, M., Zahradnik, R., and Cmuchalova, B. 1962. Influence of alcohols and potassium salts of xanthogenic acids on various biological objects. Arch Int Pharmacodyn Ther. 135: 330-343. Cited in: WHO, 1990.

Clayton, G.D. and Clayton, F.E. eds. 1994. Patty's Industrial Hygiene and Toxicology. Volume II, Part D. Toxicology. 4th Edition. John Wiley and Sons, Inc.: Toronto, ON.

Clewell, H., Gentry, P., Gearhart, J., Covington, T., Banton, M., and Andersen, M. 2001. Development of a physiologically based pharmacokinetic model of isopropanol and its metabolite acteone. Toxicol Sci (In Press). Cited in: Gentry *et al.*, 2002.

Cupitt, L.T. 1980. Fate of toxic and hazardous materials in the air environment, Research Triangle Park, North Carolina, U.S. Environmental Protection Agency, Environmental Sciences Laboratory, Office of Research and Development (EPA 600/3-80-084, PB 80-221948).

Daniel, D.R., McAnalley, B.H., and Garriot, J.C. 1981. Isopropyl alcohol metabolism after acute intoxication in humans. J. Anal Toxicol. 5: 110-112. Cited in: WHO, 1990.

David, J. and Bochquet, C. 1976. Compared toxicities of different alcohols for two Drosophila sibling species: *D. melanogaster* and *D. simulans*. Comp Biochem Physiol. 54C: 71-74. Cited in: WHO, 1990.

Davis, D.G., Wergin, W.P., and Dusbabek, K.E. 1978. Effects of organic solvents on growth and ultrastructure of plant cell suspensions. Pestic Biochem Physiol. 8: 84-97. Cited in: WHO, 1990.

Davis, P.L., Dal Cortivo, L.A., and Maturo, J. 1984. Endogenous isopropanol: Forensic and biochemical implications. J Anal Toxicol. 8:209-212. Cited in: WHO, 1990.

De Ceaurriz, J.C., Micillino, J.C., Bonnet, P., and Guenier, J.P. 1981. Sensory irritation caused by various industrial airborne chemicals. Toxicol Lett. 9: 137-143. Cited in: WHO, 1990.

Dewulf, J., Langenhove, H. V. 1997. Analytical Techniques for the Determination and Measurement Data of 7 Chlorinated C1- and C2-Hydrocarbons and 6 Monocyclic Aromatic Hydrocarbons in Remote Air Masses: An Overview. Atmospheric Environment. 31: 3291-3307.

Ellenhorn, M.J. and D.G. Barceloux. 1988. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. Elsevier Science Publishing Co. Inc.: New York, NY. Cited in: HSDB, 2003.

Enterline, P.E. 1982. Importance of sequential exposure in the production of epichlorohydrin and isopropanol. Ann N.Y. Acad Sci. 381: 344-349. Cited in: WHO, 1990.

Farley, F.F. 1977. International Conference on Photochemical Oxidant Pollution and Its Controls - Proceedings, Sep. 12-17, 1976, Raleigh, NC. U.S. Environmental Protection Agency (U.S. EPA), Raleigh, NC. U.S. EPA-600/3- 77-001b. Cited in: HSDB, 2003.

Florin, I., Rutberg, L., Curvall, M., and Enzell, C.R. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology. 18: 219-232. Cited in: WHO, 1990.

Gentry, P.R., Covington, T.R., Andersen, M.E., and Clewell, H.J. 2002. Application of a physiologically based pharmacokinetic model for isopropanol in the derivation of a reference dose and reference concentration. Reg Toxicol Pharmacol. 36: 51-68.

Ghittori S, Maestri L, Maraccini P, and Imbriani M. 1996. Acetone in Urine as Biological Index of Occupational Exposure to Isopropyl Alcohol. Industrial Health. 34 (4): 409-414.

Gill, M.W., Burleigh-Flayer, H.D., Strother, D.E., Masten, L.W., McKee, R.H., Tyler, T.R., and Gardiner, T.H. 1995. Isopropanol: Acute vapor inhalation neurotoxicity study in rats. J Appl Toxicol. 15(2):77-84.

Guseinov, V.G. 1985. Toxicological hygienic characteristics of isopropyl alcohol. Gig Tr Prof Zabol. (7): 60-62 (in Russian). Cited in: WHO, 1990.

Hermens, J., Broekhuyzen, E., Canton, H., and Wegman, R. 1985. Quantitative structure-activity relationships and mixture toxicity studies of mixtures of alcohols and chlorohydrocarbons: effects on growth of Daphnia magna. Aquat Toxicol. 6: 209-217. Cited in: WHO, 1990.

Howard, P.H. 1990. Handbook of Environmental Fate and Exposure for Organic Chemicals. Volumes 1-4. Lewis Publishers. Chelsea, MI.

Howard, P.H., Boethling, R.S., Jarvis, W.F., Meylan, W.M., and Michalenko, W. eds. 1991. Handbook of Environmental Degradation Rates. Lewis Publishers, Inc.: Chelsea, Michigan.

HSDB (Hazardous Substances Data Bank). 2003. Hazardous Substances Data Bank. Isopropanol. Toxicology Data Network System. National Library of Medicine. Bethesda, MD.

Hueper, W.C. 1966. Occupational and environmental cancers of the respiratory system. Recent results. Cancer Res. 3: 105-107. Cited in: WHO, 1990.

IARC. 1999. Isopropanol (Group 3). Re-Evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. International Agency for Research on Cancer: Lyon, France. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 71:1027.

Idota, S. 1985. Studies on isopropanol metabolism and poisoning. J Nihon Univ Med Assoc. 44:39-47 (in Japanese). Cited in: WHO, 1990.

Kane, L.E., Dombroske, R., and Alarie, Y. 1980. Evaluation of sensory irritation from some common industrial solvents. Am Ind Hyg Assoc J. 41: 451-455. Cited in: WHO, 1990.

Kapp, R.W. Jr. Marino D.J. Gardiner, T.H., Masten, L.W. Mckee, R.H. Tyler, T.R. Ivett, J.L. and Young, R.R. 1993. *In vitro* and *in vivo* assays of isopropanol for mutagenicity. Environ Mol Mutagen. 22(2): 93-100.

Kapp, R.W. Jr., Bevan C., Gardiner T.H., Banton, M.I., Tyler, T.R. and Wright, G.A. 1996. Isopropanol: summary of TSCA test rule studies and releavance to hazard identification. Regul Toxicol Pharmacol. 23(3): 183-192.

Kawai, T. Yagusi, T., Horiguchi, S., Uchida, Y. Iwami, O., Iguchi, H., Inoue, O, Watanabe, T., Nakatsuka, H., and Ikeda, M. 1990. Biological monitoring of occupational exposure to isopropyl alcohol vapor by urinalysis for acetone. Int Arch Environ Health. 62(5): 409-413.

Kemal, H. 1927. Contribution to investigations into the fate of isopropyl alcohol in the human body. Biochemische Zeitschrift. 187:461-466 (in German). Cited in: WHO, 1990.

Kirk-Othmer. 1996. Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volume 1. : John Wiley and Sons: New York, NY. Pp. V20.

Kramer, V.C., Schnell, D.J., and Nickerson, K.W. 1983. Relative toxicity of organic solvents to Aedes aegyptilarvae. J Invertebr Pathol. 42: 285-287. Cited in: WHO, 1990.

Laham, S., Potvin, M., and Schader, K. 1979. Microméthode de dosage simultané de l'alcool isopropylique et de son metabolite l'acétone. Chemosphere. 2: 79-87. Cited in: WHO, 1990.

Laham, S., Potvin, M., Schrader, K., and Marion, I. 1980. Studies on inhalation toxicity of 2-propanol. Drug Chem Toxicol. 3: 343-360. Cited in: WHO, 1990.

Leffingwell, S.S., Waxweiler, R., Alexander, V., Ludwig, H.R. and Halperin, W. 1983. Case-control study of gliomas of the brain among workers employed by a Texas City, Texas chemical plant. Neuroepidemiology. 2: 179-195. Cited in: WHO, 1990.

Lehman A.J., Schwerma H., and Rickards, E. 1944. Isopropyl alcohol: rate of disappearance from the blood stream of dogs after intravenous and oral administration. J Pharmacol Exp Ther. 82: 196-201. Cited in: WHO, 1990.

Lehman A.J., Schwerma H., and Rickards, E. 1945. Acquired tolerance in dogs, rate of disappearance from the blood stream in various species, and effects on successive generation of rats. J Pharmacol Exp. Ther. 85: 61-69. Cited in: WHO, 1990.

Lewis, G.D., Laufman, A.K., McAnalley, B.H., and Garriot, J.C. 1984. Metabolism of acetone to isopropyl alcohol in rats and humans. J Forensic Sci. 29: 541-549. Cited in: WHO, 1990.

Lewis, R.J., Sr ed. 1997. Hawley's Condensed Chemical Dictionary. 13th Edition. John Wiley and Sons, Inc.: New York, NY.

Lodge, J. P. 1988. Methods of Air Sampling and Analysis. Third Edition. Lewis Publishers. Boca Raton, FLA.

Mackay, D., Shiu, W.Y., and Ma, K.C. 1992. Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals. Volume IV. Lewis Publishers: Boca Raton.

Mattson, V.R., Arthur, J.W., and Walbridge, C.T. 1976. Acute toxicity of selected organic compounds to fathead minnows, Duluth, Minnesota. U.S. Environmental Protection Agency, Environmental Research Laboratory (EPA 600/3-76-097; PB 262897).

Nakaseko, H. 1990. Experimental studies on the toxicity of isopropyl alcohol. Osaka-shi Igakkai Zasshi 39(2):213-231.

Natowicz, M., Donahue, J., Gorman, L., Kane, M., McKissick, J. and Shaw, L. 1985. Pharmacokinetic analysis of a case of isopropanol intoxication. Clin Med. 31: 326-328. Cited in: WHO, 1990.

Nelson, B.K., Brightwell, W.S., MacKenzie-Taylor, D.R., Khan, A., Burg, J.R., Weigel, W.W., and Goad, P.T. 1988. Teratogenicity of n-propanol and isopropanol administered at high inhalation concentrations to rats. Food Chem Toxicol. 26: 247-254.

Nelson, K.W., Ege, J.F., Ross, M., Woodman, L.E., and Silverman, L. 1943. Sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol. 25: 282-285. Cited in: WHO, 1990.

NIOSH (National Institute for Occupational Safety and Health). 1994. Manual of Analytical Methods (NMAM) – 4th Edition, Volume 3, Method 1400: Alcohols 1. U.S.Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Physical Sciences and Engineering, Cincinnati, OH, 1994.

NIOSH (National Institute for Occupational Safety and Health). 1994. Manual of Analytical Methods (NMAM) – 4th Edition, Volume 3, Method 4000. U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Physical Sciences and Engineering, Cincinnati, OH.

NIOSH (National Institute for Occupational Safety and Health). 1994. Manual of Analytical Methods (NMAM) – 4th Edition, Volume 3, Method 1500. U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Physical Sciences and Engineering, Cincinnati, OH.

NIOSH (National Institute for Occupational Safety and Health). 1994. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Publication No. 94-116. U.S. Government Printing Office: Washington, D.C, June 1994.

NIOSH (National Institute for Occupational Safety and Health). 1996. Manual of Analytical Methods (NMAM) – 4th Edition, Volume 3, Method 2549: Volatile Organic Compounds (Screening). U.S.Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Physical Sciences and Engineering, Cincinnati, OH, 1996.

NIOSH (National Institute for Occupational Safety and Health). 2003. Chemical listing and documentation of revised IDLH values (Accessed November 2003). http://www.cdc.gov/niosh/intridl4.html

NJDHSS (New Jersey Department of Health and Senior Services). 1997. Hazardous Substances Fact Sheet. Isopropyl Alcohol. January 1997. http://www.state.nj.us/health/eoh/rtkweb/rtkhsfs.htm#I

Nordmann, R., Ribiere, C., Rouach, H., Beage, F., Giudicelli, Y., and Nordmann, J. 1973. Metabolic pathways involved in the oxidation of isopropanol into acetone by the intact rat. Life Sci. 13:919-932. Cited in: WHO, 1990.

NPRI (National Pollutant Release Inventory). 2001. NPRI Data Search. Isopropyl Alcohol. http://www.ec.gc.ca/pdb/querysite/html

NTP (National Toxicology Program). 2001. Chemical Health and Safety Data, Chemical Repository, Isopropanol. http://ntp-server.niehs.nih.gov/Main_Pages/Chem-HS.html

OEHHA (Office of Environmental Health Hazard Assessment). 1999. Determination of Acute Reference Exposure Levels for Airborne Toxicants. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency

OEHHA (Office of Environmental Health Hazard Assessment). 1999. Acute Toxicity Summary: Isopropyl Alcohol. Determination of Acute Reference Exposure levels for Airborne Toxicants. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency, March, 1999.

OEHHA (Office of Environmental Health Hazard Assessment). 2003. Chronic Toxicity Summary. Isopropanol. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency http://www.oehha.org/air/chronic_rels/pdf/67630.pdf.

Ohashi, Y., Nakai, Y., Ikeoka, H., Koshimo, H., Esaki, Y., Horiguchi, S., Teramoto, K., and Nakaseko, H. 1987a. Recovery process of tracheal mucosa of guinea-pigs exposed to isopropyl alcohol. Arch Toxicol. 61: 12-20.

Ohashi, Y., Nakai, Y., Ikeoka, H., Koshimo, H., Esaki, Y., Horiguchi, S., Teramoto, K., and Nakaseko, H. 1987b. Acute effects of isopropyl alcohol exposure on the middle ear mucosa. J Appl Toxicol. 7: 205-211.

OMOE (Ontario Ministry of the Environment). 2002. Information Draft on the Development of Air Standards for Isopropanol. Standards Development Branch Ontario Ministry of the Environment, December 2002.

OSHA (Occupational Safety and Health Administration). 1994. OSHA Sampling and Analytical Methods, Organic Method 111. U.S. Department of Labor, Occupational Safety and Health Administration, Organic Methods Evaluation Branch, OSHA Salt Lake Technical Center, Salt Lake City, UT, December 1994

OSHA (Occupational Safety and Health Administration). 1997. OSHA Sampling and Analytical Methods, Organic Method 109. U.S. Department of Labor, Occupational Safety and Health Administration, Organic Methods Evaluation Branch, OSHA Salt Lake Technical Center, Salt Lake City, UT, June 1997.

OSHA (Occupational Safety and Health Administration). 1998. OSHA Sampling and Analytical Methods, Organic Method 111. U.S. Department of Labor, Occupational Safety and Health Administration, Organic Methods Evaluation Branch, OSHA Salt Lake Technical Center, Salt Lake City, UT, April 1998.

OSHA (Occupational Safety and Health Administration). 2000. OSHA Sampling and Analytical Methods, Organic Method 07. U.S. Department of Labor, Occupational Safety and Health Administration, Organic Methods Evaluation Branch, OSHA Salt Lake Technical Center, Salt Lake City, UT, May 2000.

Price, K.S., Waggy, G.T., and Conway, R.A. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. J Water Pollut Control Fed. 46: 63-77. Cited in: WHO, 1990.

Raichle, M.E., Eichling, J.O., Straatmann, M.G., Welch, M.J., Larson, K.B., and Ter-Pogossian, M.M. 1976. Blood-brain barrier permeability of 11C-labeled alcohols and 15U-labeled water. Am J Physiol. 230: 542-552. Cited In: WHO, 1990.

RAIS (Risk Assessment Information System). 2003. Chemical-Specific Toxicity Values, Isopropanol. http://risk.lsd.ornl.gov/cgi-bin/tox/TOX_select?select=nrad

Ray, S.D. and Mehendale, H.M. 1990. Potential of CC14 hepatotoxicity and lethality by various alcohols. Fundam Appl. Toxicol. 15(3): 429-440.

Reynolds, T. 1977. An anomalous effect of isopropanol on lettuce germination. Plant Sci Lett. 15: 25-28. Cited in: WHO, 1990.

Rietbrock, N. and Abshagen, U. 1971. Pharmacokinetics and metabolism of aliphatic alcohols. Arzneim.-Forsch. 21: 1309-1319 (in German). Cited in: WHO, 1990.

Rowe, V.K., and McCollister, S.B. 1982. Alcohols. In: Clayton, G.D., and Clayton, F.E., Eds. Patty's Industrial Hygiene and Toxicology, 3rd Edition. Volume 2C, Toxicology. John Wiley and Sons: New York, N.Y. Pp. 4561-4571

Savolainen H., Pekari, K., and Helojoki, H. 1979. Neurochemical and behavioural effects of extended exposure to isopropanol vapour with simultaneous ethanol intake. Chem Biol Interact 28: 237-248.

Sethre, T., Laubli, T., Berode, M. and Krueger, H. 2000a. Neurobehavioural effects of experimental isopropanol exposure. International Archives of Occupational and Environmental Health 73:105-112.

Sethre, T., Laubli, T., Hangartner, M., Berode, M. and Krueger, H. 2000b. Isopropanol and methylformate exposure in a foundry: exposure data and neurobehavioural measurements. International Archives of Occupational and Environmental Health 73:528-536.

Siebert, H., Siebert, G., and Bohn, G. 1972. Animal experimental investigations into the metabolism of propan-2-ol. Deutsche Apotheker Zeitung. 112:1040-1041 (in German). Cited in: WHO, 1990.

Slauter, R.W., Coleman, D.P., Gaudette, N.F., McKee, R.H., Masten, L.W., Gardiner, T.H., Strother, D.E., Tyler, T.R., and Jeffcoat, A.R. 1994. Disposition and pharmacokinetics of isopropanol in F-344 rats and B6C3F1 mice. Fundam Appl Toxicol. 23(3):407-420.

Smeets, M., and Dalton, P. 2002. Perceived odor and irritation of isopropanol: a comparison between naive controls and occupationally exposed workers. Int Arch Occup Environ Health. 75(8):541-8.

Smyth, H.F. 1956. Improved communication: Hygienic standards for daily inhalation. Am Ind Hyg Assoc Q. 17(2): 129-185. Cited in: ACGIH, 1992.

Snyder, R., ed. 1992. Ethel Browning's Toxicity and Metabolism of Industrial Solvents. Second Edition. Volume 3 Alcohols and Esters. Elsevier: New York, N.Y. Cited in: HSDB, 2003.

Teramoto, K., Wakitani, F., Horiguchi, S., Jo, T., Yamamoto, T., Mitustake, H., and Nakseko, H. 1993. Comparison of the neurotoxicity of several chemicals estimated by the peripheral nerve conduction velocity in rats. Environ Res. 62:407-420. Cited in: OEHHA, 2003.

Tiess and Hammer, U. 1985. On endogenous acetone (propane-2-on) and isopropanol (propane-2-ol) levels in the human body after ketoacidic states. Z. gesamte Hyg. 31: 527-529 (in German). Cited in: WHO, 1990.

Tomita, M. and Nishimura, M. 1982. Using saliva to estimate human exposure to organic solvents. Bull Tokyo Dent Coll. 23: 175-188. Cited in: WHO, 1990.

Tooby, T.E., Hursey, P.A., and Alabaster, J.S. 1975. The acute toxicity of 102 pesticides and miscellaneous substances to fish. Chem Ind. 12: 523-526. Cited in: WHO, 1990.

Tyl, R.W., Masten, L.W., Marr, M.C., Myers, C.B., Slauter, R.W., Gardiner, T.H., Strother, D.E., McKee, R.H., and Tyler, T.R. 1994. Developmental toxicity evaluation of isopropanol by gavage in rats and rabbits. Fundam Appl Toxicol. 22(1):139-151.

U.S. EPA. 1984. Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air, 2nd Edition (TO-1). U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory, Center for Environmental Research Information: Cincinnati, OH. April 1984.

U.S. EPA. 1999. Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air, 2nd Edition (TO-14A). U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory, Center for Environmental Research Information: Cincinnati, OH. January 1999.

U.S. EPA. 1999. Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air, 2nd Edition (TO-15). U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory, Center for Environmental Research Information: Cincinnati, OH. January 1999.

U.S. EPA. 1999. Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air, 2nd Edition (TO-17). U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory, Center for Environmental Research Information: Cincinnati, OH. January 1999.

U.S. EPA. 1999a. Compendium Method TO-14A: Determination of volatile organic compounds in ambient air using specially prepared canisters with subsequent analysis by gas chromatography (GC). Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air – 2nd Edition. U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory, Center for Environmental Research Information. Cincinnati, OH. January 1999.

U.S. EPA. 1999b. Compendium Method TO-17: Determination of volatile organic compounds in ambient air using active sampling onto sorbent tubes. Compendium of Methods for the Determination of Toxic Organic Compounds in Ambient Air – 2nd Edition. U.S. Environmental Protection Agency, Office of Research and Development, National Risk Management Research Laboratory, Center for Environmental Research Information. Cincinnati, OH. January 1999.

U.S. EPA/OTS. 1986. A pilot one generation study with isopropyl alcohol in rats (final report) with attachments and cover letter dated 013092. EPA/OTS Doc. #86-920000728. Prepared by British Industrial Biological Research Association. Submitted by Chemical Manufacturers Association. Fiche No. NTIS/OTS0535607.

U.S. EPA/OTS. 1992a. A teratology study with isopropyl alcohol in rats. Letter submitting one enclosed teratology study and one enclosed supplementary study on isopropanol. EPA/OTS Doc. #86-920000727. Prepared by British Industrial Biological Research Association. Submitted by Chemical Manufacturers Association. Fiche No. NTIS/OTS0535606.

U.S. EPA/OTS. 1992b. Investigations supplementary to studies with isopropyl alcohol. Letter submitting one enclosed teratology study and one enclosed supplementary study on isopropanol. EPA/OTS Doc. #86-A-98 Isopropanol 920000727. Prepared by British Industrial Biological Research Association. Submitted by Chemical Manufacturers Association. Fiche No. NTIS/OTS0535604.

van Gemert, L.J. 1999. Compilations of odour threshold values in air and water. TNO Nutrition and Food Research Institute, Boelens Aroma Chemical Information Service (BACIS): Netherlands.

van Thriel C, Kiesswetter E, Blaszkewicz M, Golka K, and Seeber A. 2003. Neurobehavioral effects during experimental exposure to 1-octanol and isopropanol. Scand J Work Environ Health. 29(2):143-51.

Veith, G.D. and Kosian, P. 1983. Estimating bioconcentration potential from octanol/water partition coefficients. In: Mackay *et al.*, ed. Physical behaviour of PCBs in the Great Lakes, Ann Arbor, Michigan, Ann Arbor Science. Pp. 269-282. Cited in: WHO, 1990.

Verschueren, K., ed. 1983. Handbook of Environmental Data on Organic Chemicals (2nd Ed.). Van Nostrand Reinhold Co.: New York, NY.

Von Der Hude, W., Scheutwinkel, M., Gramlich, U., Fissler, B., and Busler, A. 1987. Genotoxicity of three carbon compounds evaluated in the SCE test *in vitro*. Environ.Mutagen. 9: 401-410.

Wax, J., Ellis, F.W., and Lehman, A.J. 1949. Absorption and distribution of isopropyl alcohol. J Pathol Exper Therapeut. 97: 229-237. Cited in: WHO, 1990.

Weil, C.S., Smyth, H.F., and Nale, T.W. 1952. Quest for a suspected industrial carcinogen. Arch Ind Hyg Occup Med. 5: 535-547. Cited in: WHO, 1990.

WHO (World Health Organization). 1990. 2-Propanol. World Health Organization, International Programme on Chemical Safety (WHO): Geneva, Switzerland. Environmental Health Criteria 103.

Wright, U. 1979. The hidden carcinogen in the manufacture of isopropyl alcohol. Dev Toxicol Environ Sci. 4: 93-98. Cited in: WHO, 1990.

Yanagihara, S., Shimada, I., Shinoyama, E., Chisaka, F., and Saito, K. 1977. Photochemical reactivities of hydrocarbons. Proc Int Clean Air Congr. 4: 472- 477. Cited in: HSDB, 2003.

Zahlsen, K., Aarstad, K., and Nilsen, O.G. 1985. Inhalation of isopropanol: induction of activating and deactivating enzymes in rat kidney and liver, increased microsomal metabolism of n-hexane. Toxicology. 34: 57-66. Cited in: WHO, 1990.

APPENDIX A

Review of Air Quality Guidelines for Isopropanol Used by Agencies in North America and Elsewhere

Agency: California Environmental Protection Agency (Cal EPA), Office of Environmental Health Hazard Assessment (OEHHA)
Guideline Value(s): Acute reference exposure level (REL) = 3,200 $\mu g/m^3$. Chronic reference exposure level (REL) = 7,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Acute REL = one-hour averaging time. Chronic REL = continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: RELs are for use in facility health risk assessments conducted for the AB 2588 Air Toxics "Hot Spots" Program.
Scientific Basis for Guideline Development: The acute REL was developed from a NOAEL of 200 ppm for mild irritation of the eyes, nose and throat in humans. The Cal EPA extrapolated a one-hour concentration based on the experimental exposure duration and applied an uncertainty factor of 10 to account for intraspecies variation. The chronic REL was developed from a NOAEL of 504 ppm for kidney and developmental effects in rats and mice. The Cal EPA adjusted the NOAEL to an average experimental exposure based on the experimental exposure duration and applied an uncertainty factor of 30 to account for interspecies and intraspecies variation.
Status of Guideline (Date of Last Revision or Update): Acute REL = May 2000. Chronic REL = September 2002.
Additional Comments: None
References and Supporting Documentation: California Environmental Protection Agency (Cal EPA). 2000. Acute Toxicity Summary for Isopropyl Alcohol. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, May 2000. URL: http://www.oehha.org/air/acute_rels/allAcRELs.html (accessed 11 November 2003). California Environmental Protection Agency (Cal EPA). 2002. Chronic Toxicity Summary for Isopropanol. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, September 2002. URL: http://www.oehha.org/air/chronic_rels/AllChrels.html (accessed 11 November 2003).

Agency: Government of Canada.
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Government of Canada. 1996. Health-Based Tolerable Daily Intakes/ Concentrations and Tumorigenic Doses/ Concentrations for Priority Substances. Government of Canada, Health Canada, Environmental Health Directorate, Health Protection Branch. Ottawa, ON. Government of Canada. 1999. Canadian National Ambient Air Quality Objectives (NAAQOs): Process and Status. Government of Canada, Environment Canada, Canadian Council of Ministers of the Environment (CCME). Ontario, Canada. Government of Canada. 2003. Priority Substance Lists (PSLs). Government of Canada, Environment Canada, CEPA Environmental Registry. URL: http://www.ec.gc.ca/CEPARegistry/subs_list/Priority.cfm (accessed 13 November 2003).

Agency: Louisiana Department of Environmental Quality (DEQ).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Louisiana Department of Environmental Quality (DEQ). 2003. Title 33 Environmental Quality, Part III Air, Chapter 51: Comprehensive Toxic Air Pollutant Emission Control Program. Louisiana Department of Environmental Quality (DEQ). Baton, LA.

Agency: Massachusetts Department of Environmental Protection (DEP).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Massachusetts Department of Environmental Protection (DEP). 1995. Massachusetts Allowable Threshold Concentrations (ATCs). Commonwealth of Massachusetts, Executive Office of Environmental Affairs, Department of Environmental Protection. Boston, MA.

Agency: Michigan Department of Environmental Quality (DEQ).
Guideline Value(s): Initial threshold screening level (ITSL) = 220 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: ITSL = 24-hour averaging time.
Application / How Guideline is Used by Agency: Michigan air toxic rules require that each source must apply the best available control technology for toxics (T-BACT) and that the emissions of the toxic air contaminant cannot result in a maximum ambient concentration that exceeds the applicable health based screening levels (*i.e.*, ITSL, IRSL, and SRSL). ITSLs are required for any new or modified emissions source or sources for which a permit to install is requested and which emits a toxic air contaminant.
Scientific Basis for Guideline Development: The ITSL was established by Michigan DEQ toxicologists based on available inhalation toxicity data and the procedures identified in Rule 229.
Status of Guideline (Date of Last Revision or Update): August 1993.
Additional Comments: The Initial Threshold Screening Level (ITSL) is defined as the health based screening level for non-carcinogenic effects of a toxic air contaminant. It is determined by a number of different methods, depending upon the available toxicological data. The rules specify a hierarchy of methods for determining the ITSL. There are two health based screening levels for carcinogenic effects. These include the Initial Risk Screening Level (IRSL), which is defined as an increased cancer risk of one in one million (10^{-6}), and the Secondary Risk Screening Level (SRSL), which is defined as an increased cancer risk of one in one hundred thousand (10^{-5}). The IRSL applies only to the new or modified source subject to the permit application. If the applicant cannot demonstrate that the emissions of the toxic air contaminant meet the IRSL, they may choose to demonstrate compliance with the SRSL, however in this case they must include all sources of that toxic air contaminant emitted from the plant, not just the emission unit being permitted.
References and Supporting Documentation: Michigan Department of Environmental Quality (DEQ). 2003. Final Screening Level List. Table 2. Michigan Department of Environmental Quality (DEQ). Air Quality Division. URL: http://www.michigan.gov/deq/0,1607,7-135-3310_4105---,00.html (accessed 12 November 2003). Michigan Department of Environmental Quality (DEQ). 2002. Procedures for Developing Screening Levels. Michigan Department of Environmental Quality (DEQ). Air Quality Division. Lansing, Michigan.

Agency: Minnesota Department of Health (MDH).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Minnesota Department of Health (MDH). 2003. Health Risk Values for Air. Minnesota Department of Health (MDH), Environmental Health in Minnesota. URL: http://www.health.state.mn.us/divs/eh/air/hrvtablepr.htm (accessed 12 November 2003).

Agency: Netherlands Research for Man and Environment (RIVM).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Research for Man and Environment (RIVM). 2001. RIVM Report 711701 025 Re-evaluation of Human-toxicological Maximum Permissible Risk Levels. URL: http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf (accessed 13 November 2003).

Agency: Newfoundland and Labrador Department of the Environment.
Guideline Value(s): 24-hour air quality standard = 24,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: The minister under the Executive Council Act uses the values prescribed in the Criteria for Acceptable Air Quality for controlling air quality, where the amount of air contaminants in the atmosphere due to all sources shall not exceed these values (*i.e.*, air quality standards).
Scientific Basis for Guideline Development: Scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): May 2003.
Additional Comments: n/a
References and Supporting Documentation: Newfoundland and Labrador Air Pollution Control Regulations. 2003. Newfoundland and Labrador Regulation 56/03. Government of Newfoundland and Labrador, Queen's Printer, May 2003.

Agency: New Hampshire Department of Environmental Services (DES).
Guideline Value(s): 24-hour ambient air limit (AAL) = 4,945 $\mu g/m^3$. Annual ambient air limit (AAL) = 3,296 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: AALs are used by the New Hampshire DES to review permit applications for sources that emit this chemical to the atmosphere. Sources are regulated through a state-wide air permitting system and include any new, modified, or existing stationary source, area source, or device.
Scientific Basis for Guideline Development: The 24–hour AAL was derived from the threshold limit value time weighted average (TLV-TWA) of 400 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. The New Hampshire DES applied a time adjustment factor of 2.8 to the TLV-TWA to account for the potentially differing effects of isopropyl alcohol over time. In addition, the New Hampshire DES incorporated a safety factor of 71 in order to adequately protect sensitive populations. The annual AAL was based on the threshold limit value time weighted average (TLV-TWA) of 400 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. The New Hampshire DES divided the occupational exposure limit by a factor of 4.2 and applied a safety factor of 71 to account for sensitive populations within the general public.
Status of Guideline (Date of Last Revision or Update): March 1997.
Additional Comments: n/a
References and Supporting Documentation: New Hampshire Department of Environmental Services (DES). New Hampshire Code of Administrative Rules. Chapter Env-A 1400. Regulated Toxic Air Pollutants. New Hampshire Department of Environmental Services (DES). Concord, NH.

Agency: New Jersey Department of Environmental Protection (DEP).
Guideline Value(s): Short-term reference concentration (RfC) = 3,200 µg/m^3. Reference concentration (RfC) = 7,000 µg/m^3.
Averaging Time to Which Guideline Applies: Short-term RfC = one-hour averaging time. RfC = continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: RfCs are used by the New Jersey DEP to review permit applications for sources that emit isopropanol to the atmosphere.
Scientific Basis for Guideline Development: The one-hour RfC and the annual RfC are based on the reference concentrations (RfCs) of 3,200 µg/m^3 and 7,000 µg/m^3, respectively, established by Cal EPA.
Status of Guideline (Date of Last Revision or Update): April 2003.
Additional Comments: n/a
References and Supporting Documentation: New Jersey Department of Environmental Protection (DEP). 2003. Reference Concentrations for Short-Term Inhalation Exposure. New Jersey Department of Environmental Protection (DEP), Division of Air Quality, Bureau of Air Quality Evaluation. April 2003. New Jersey Department of Environmental Protection (DEP). 1994. Technical Manual 1003: Guidance on Preparing a Risk Assessment for Air Contaminant Emissions. New Jersey Department of Environmental Protection (DEP), Air Quality Permitting Program, Bureau of Air Quality Evaluation. Revised December 1994.

Agency: New York State Department of Environmental Conservation (DEC).
Guideline Value(s): Short-term guideline concentration (SGC) = 120,000 $\mu g/m^3$. Annual guideline concentration (AGC) = 7,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: SGC = one-hour averaging time. AGC = continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: SGCs and AGCs are used by the New York State DEC to review permit applications for sources that emit isopropanol to the atmosphere.
Scientific Basis for Guideline Development: The SGC was derived from the threshold limit value short-term exposure limit (TLV-STEL) of 500 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. A safety factor of 10 was applied to the STEL by the NY DEC to account for sensitive individuals in the general population. The AGC for isopropyl alcohol was independently derived by the NY State DEC to protect the general population from adverse inhalation exposure at off-site industrial property. The specific scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): July 2000.
Additional Comments: n/a
References and Supporting Documentation: New York State Department of Environmental Conservation (DEC). 2000. DAR – 1 AGC/SGC Tables includes TLVs & STELs for the Year 2000. New York State Department of Environmental Conservation, Division of Air Resources, Bureau of Stationary Sources. Albany, NY.

Agency: North Carolina Department of Environment and Natural Resources (ENR).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: North Carolina Department of Environment and Natural Resources (ENR). 2002. North Carolina Air Quality Rules 15A NCAC 2D (Air Pollution Control Requirements) and 15A NCAC 2Q (Air quality Permit Procedures). Section .1100 – Control of Toxic Air Pollutants. North Carolina Department of Environment and Natural Resources. Raleigh, NC.

Agency: Ohio Environmental Protection Agency (EPA)
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Ohio Environmental Protection Agency (EPA). 2002. Review of New Sources of Air Toxic Emissions. Option A. Ohio Environmental Protection Agency, Division of Air Pollution Control. Columbus, Ohio.

Agency: Oklahoma Department of Environmental Quality (DEQ).
Guideline Value(s): Maximum acceptable ambient air concentration (MAAC) = 98,339 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: 24-hour averaging time.
Application / How Guideline is Used by Agency: MAACs are used by Oklahoma DEQ to review permit applications of sources that emit isopropanol to the atmosphere.
Scientific Basis for Guideline Development: The 24-hour MAAC was based on the threshold limit value time weighted average (TLV-TWA) of 400 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH). A safety factor of 10 was incorporated by the Oklahoma DEQ.
Status of Guideline (Date of Last Revision or Update): November 2003.
Additional Comments: n/a
References and Supporting Documentation: Oklahoma Department of Environmental Quality (DEQ). 2003. Total Air Toxics Partial Listing. Oklahoma Department of Environmental Quality. URL: http://www.deq.state.ok.us/AQDnew/toxics/listings/pollutant_query_1.html (accessed 12 November 2003). Oklahoma Department of Environmental Quality (DEQ). Title 252. Department of Environmental Quality Chapter 100. Air Pollution Control. 100:252-41: Control of Emission of Hazardous and Toxic Air Contaminants. Oklahoma Department of Environmental Quality. Oklahoma City, OK.

Agency: Ontario Ministry of Environment and Energy (OMEE).
Guideline Value(s): 24-hour ambient air quality criteria (AAQC) = 24,000 $\mu g/m^3$. Half-hour point of impingement (POI) = 24,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: AAQC are used by OMEE to represent human health or environmental effect-based values not expected to cause adverse effects based on continuous exposure. AAQC are not used by OMEE to permit stationary sources that emit this chemical into the environment. The 30-minute POI is used by OMEE to review permit applications for stationary sources that emit this chemical to the environment.
Scientific Basis for Guideline Development: Both the 24-hour AAQC and the half-hour POI standards were developed based on the odour effects of isopropanol, where odour thresholds range from 8,000 $\mu g/m^3$ to 1,500,000 $\mu g/m^3$. The specific scientific basis for the guidelines' development was not provided.
Status of Guideline (Date of Last Revision or Update): December 2002.
Additional Comments: The half-hour POI for isopropanol is defined as a guideline value by OMEE.
References and Supporting Documentation: Ontario Ministry of Environment and Energy (OMEE). 2001. Summary of Point of Impingement Standards, Point of Impingement Guidelines, and Ambient Air Quality Criteria (AAQCs). Standards Development Branch, Ontario Ministry of the Environment, September 2001. Ontario Ministry of Environment and Energy (OMEE). 2001. Information Draft on the Air Standards for Isopropanol. Standards Development Branch, Ontario Ministry of the Environment, December 2002.

Agency: Government of Quebec.
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Government of Quebec. 2002. Air Quality Criteria. Government of Quebec, Ministry of the Environment. URL: http://www.menv.gouv.qc.ca/air/criteres/fiches.pdf (accessed 13 November 2003).

Agency: Texas Natural Resource Conservation Commission (TNRCC).
Guideline Value(s): Short-term effects screening level (ESL) = 7,850 $\mu g/m^3$. Long-term effects screening level (ESL) = 785 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Short-term ESL = one-hour averaging time. Long-term ESL = annual averaging time.
Application / How Guideline is Used by Agency: ESLs are used to evaluate the potential for effects to occur as a result of exposure to concentrations of constituents in the air. ESLs are based on data concerning health effects, odour nuisance potential, effects with respect to vegetation, and corrosion effects. They are not ambient air standards. If predicted or measured airborne levels of a constituent do not exceed the screening level, adverse health or welfare effects would not be expected to result. If ambient levels of constituents in air exceed the screening levels, it does not necessarily indicate a problem, but rather, triggers a more in-depth review.
Scientific Basis for Guideline Development: Both the short-term and long-term ESLs for isopropanol were developed based on odour nuisance potential, specifically 50% of the odour threshold concentration.
Status of Guideline (Date of Last Revision or Update): October 2003.
Additional Comments: n/a
References and Supporting Documentation: Texas Natural Resource Conservation Commission (TNRCC). 2003. Effects Screening Levels List. URL: http://www.tnrcc.state.tx.us/permitting/tox/esl.html (accessed 13 November 2003).

Agency: U.S. Agency for Toxic Substances and Disease Registry (ATSDR).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: U.S. Agency for Toxic Substances and Disease Registry (ATSDR). 2003. Toxicological profiles. URL: http://www.atsdr.cdc.gov/toxpro2.html (accessed on 11 November 2003).

Agency: U.S. Environmental Protection Agency (EPA).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: U.S. Environmental Protection Agency (EPA). 2003. Integrated Risk Information System (IRIS). URL: http://www.epa.gov/iris/index.html (accessed 11 November 2003).

Agency: Vermont Agency of Natural Resources (ANR).
Guideline Value(s): Short-term hazardous ambient air standard (HAAS) = 98,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Eight-hour averaging time.
Application / How Guideline is Used by Agency: HAASs are used by Vermont ANR to review permit applications for stationary sources that emit isopropyl alcohol to the atmosphere.
Scientific Basis for Guideline Development: The eight-hour HAAS was based on the threshold limit value time weighted average (TLV-TWA) of 400 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. A safety factor of 10 was incorporated by the Vermont ANR.
Status of Guideline (Date of Last Revision or Update): November 2001.
Additional Comments: The Vermont ANR classified isopropyl alcohol as a non-carcinogen considered to have only short-term irritant effects.
References and Supporting Documentation: Vermont Agency of Natural Resources (ANR). 2001. Air Pollution Control Regulations, Including Amendments to the Regulations Through: November 29, 2001. Vermont Agency of Natural Resources, Air Pollution Control Division, Department of Environmental Conservation, Agency of Natural Resources. Waterbury, Vermont.

Agency: Washington Department of Ecology (DOE).
Guideline Value(s): Acceptable source impact level (ASIL) = 3,300 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: 24-hour averaging time.
Application / How Guideline is Used by Agency: ASILs are used Washington DOE to review permit applications for stationary sources that emit isopropyl alcohol to the atmosphere.
Scientific Basis for Guideline Development: The 24-hour ASIL for isopropyl alcohol is based on the threshold limit value time weighted average (TLV-TWA) of 400 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. The Washington DOE divided the TLV-TWA by three to calculate the 24-hour TWA acceptable source impact level.
Status of Guideline (Date of Last Revision or Update): October 1998.
Additional Comments: n/a
References and Supporting Documentation: Washington Department of Ecology (DOE). 1998. Chapter 173-460 WAC. Controls for New Sources of Toxic Air Pollutants. Washington Department of Ecology (DOE). Olympia, WA.

Agency: World Health Organization (WHO).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: World Health Organization (WHO). 1999. Air Quality Guidelines. Chapter 3: Health-based Guidelines. World Health Organization, Geneva.